Original Research Article

Dementia and Geriatric Cognitive Disorders

Dement Geriatr Cogn Disord 2011;31:233–238
DOI: 10.1159/000326214

Accepted: February 17, 2011
Published online: April 7, 2011

Measuring Therapeutic Efficacy in Patients with Alzheimer's Disease: Role of Instruments

Matthias W. Riepe[a] Wolfgang Janetzky[b] Ole M. Lemming[c]

[a]Department of Psychiatry and Psychotherapy II, Mental Health and Old Age Psychiatry, Ulm University, Ulm, and [b]Lundbeck GmbH Germany, Scientific Unit, Hamburg, Germany; [c]Lundbeck A/S, Scientific Unit, Valby, Denmark

Key Words
Alzheimer's disease · Cognition · Meta-analysis · Effect size

Abstract
Background/Aims: Global cognitive scales and meta-analyses thereof are used to appraise therapeutic efficacy over a broad range of disease severity. Clinically, however, different aspects of cognition change in different stages of disease. ***Methods:*** Calculation of effect sizes for single cognitive functions on treatment as assessed by the Alzheimer's Disease Assessment Scale (ADAS-cog), the Mini-Mental-Status Examination (MMSE), and the Severe Impairment Battery (SIB). In these scales, subdomains of 'cognition', e.g. memory and language, are represented in different proportions. To exemplify the analysis of 'cognition', we used original data of previously published clinical studies with memantine. ***Results:*** Depending on dementia severity and on the scale used, the effect size for memory varies between –0.44 and +0.34 and for language between –0.40 and +0.26. ***Conclusion:*** Beyond interstudy variance, effect sizes for treatment with antidementia drugs are subject to disease stage, instruments used, and interaction thereof. Therefore, clinical interpretation is necessary to appraise therapeutic efficacy in clinical studies and meta-analyses thereof when patients with different severity are included or different instruments are used. Alternatively, severity-adapted endpoints should be used for appraisal and meta-analysis of therapeutic efficacy.

Background

Prevalence of Alzheimer's disease (AD) and other dementias are increasing in the aging societies of the Western hemisphere. The duration of dementia from the mild to the severe stage is several years. Patients remain in each stage for about 3–5 years with a slow and steady decline of function in AD. Currently, most clinical studies are performed in the mild-to-moderate stage of disease or in moderate-to-severe stage of disease. To measure the efficacy, clinical studies employ a variety of instruments. For a multitude of reasons the numerical results of clinical studies comparing different treatments vary. Meta-analyses on standardized mean differences are performed in recent times to account for variance of the magnitude of effects in clinical studies. In dementia research, meta-analyses pertain to the assessment of 'cognition', 'behavior', and 'activities of daily living'. These, however, are

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

1420–8008/11/0313–0233$38.00/0

Accessible online at:
www.karger.com/dem

Prof. Matthias W. Riepe, MD
Division of Mental Health and Old Age Psychiatry, Psychiatry II, University of Ulm
Ludwig-Heilmeyer-Strasse 2
DE–89312 Günzburg (Germany)
Tel. +49 8221 96 2355, E-Mail matthias.riepe@uni-ulm.de

composite measures, e.g. 'cognition' comprises single cognitive functions such as memory, orientation, and language.

In clinical studies, 'cognition' is measured with standardized composite scales. Most frequently used are the Alzheimer's Disease Assessment Scale (ADAS-cog) [21], the Mini-Mental-Status Examination (MMSE) [6], and, more recently, in advanced stages of dementia, the Severe Impairment Battery (SIB) [24]. To interpret the findings using these composite scales, one needs to bear in mind that overall decline in the composite endpoint results from decline of function in different domains. With advancing severity of dementia the spectrum of symptoms changes so that a reduction of the total MMSE score reflects impairment of memory in early stages of disease but loss of function in other cognitive domains in later stages [2]. For instance, a three-point loss in the MMSE score likely indicates impairment of memory in mild AD (MMSE >20) while a loss of three points in severe AD (MMSE <10) may reflect apraxia or other symptoms. Considering the difference in underlying neural networks, it is likely that sensitivity to change on enhancement of neurotransmission is different for these aspects even though they are summarized as 'cognition'. It has already been reported that the ADAS-cog and its subscales provide maximum information at moderate levels of cognitive dysfunction [3]. Raw score differences toward the lower and higher ends of the scale corresponded to large differences in cognitive dysfunction, whereas raw score differences toward the middle of the scale corresponded to smaller differences [3]. In fact, in more severe stages of disease the ADAS-cog loses its sensitivity of change so much that the severe impairment battery was developed to assess patients who are unable to complete tests such as the ADAS-cog [24].

It was the goal of the present analysis to assess how mean weighted differences are affected by the interaction of instrument and disease severity. To achieve this we analyzed subscales of established instruments (ADAS-cog, MMSE, SIB) targeting similar functions (memory, orientation, language) in patients with moderate-to-severe AD treated with memantine.

Methods

Patients and Clinical Studies

Only two clinical studies used parallel instruments to target 'cognition' in patients with dementia treated with memantine. The analyses in this manuscript were calculated from the original data of two clinical studies conducted in the USA, study 9605 [19] and MD-12 [18]. Study 9605 was sponsored by Merz Pharmaceuticals GmbH, took place from 1998–1999 and had a total population size of 252 patients (126 randomized for memantine, 126 for placebo) with probable AD with moderate-to-severe to severe dementia (MMSE range 3–14). Outcome measures in this study were the Clinician's Interview-Based Impression of Change Plus Caregiver Input (NYU-CIBIC-Plus), the ADCS-ADL modified for more severe dementia (ADCS-ADLsev), the SIB, the MMSE, the Global Deterioration Scale, the Functional Assessment Scale (FAST), the Neuropsychiatric Inventory (NPI), and the Resource Utilization in Dementia (RUD). Study MD-12 was sponsored by Forest Laboratories Inc., took place from 2002–2003 and had a total population size of 433 patients (217 randomized for memantine and 216 for placebo) with probable AD with mild-to-moderate dementia (MMSE range 10–22) and included only patients already on stable medication with acetylcholinesterase inhibitor. Outcome measures in this study were the Clinician's Interview-Based Impression of Change Plus Caregiver Input (ADCS-CGIC-CIBIC-Plus), the MMSE, the cognitive part of the ADAS-cog, the NPI, the ADCS-ADL, and the RUD. For the present analysis, only patients in-label for prescription of memantine, i.e. with an MMSE score between 10 and 19, were included.

Mini-Mental Status Examination

The MMSE [6] score is between 0 and 30 (best) with subscales orientation (0–10), language (0–7), memory (0–6), attention (0–5), and motor/constructional (0–2).

Alzheimer's Disease Assessment Scale

The ADAS-cog [21] score is between 0 and 70 (worst) with subscales memory (0–27; word recall (0–10), word recognition (0–12), remembering test instructions (0–5)), orientation (0–8), language (0–25; naming (0–5), following commands (0–5), spoken language ability (0–5), word finding difficulty (0–5), language comprehension (0–5)), praxis (0–10; copy drawings (0–5), and ideational praxis (0–5)).

Severe Impairment Battery

The SIB [24] score is between 0 and 100 (best) with subscales attention (0–6), orientation (0–6), language (0–46), memory (0–14), visuospatial ability (0–8), praxis (0–8), construction (0–4), social interaction skills (0–6), and orienting to name (0–2).

Patients

Only two clinical studies used parallel instruments to target 'cognition' in patients with dementia treated with memantine. One study assessed the efficacy of memantine treatment versus placebo treatment in patients with moderate-to-severe to severe AD [19], the other study analyzed treatment with memantine versus placebo in mild-to-moderate AD patients receiving stable dose of acetylcholinesterase inhibitor [18]. The original data of these clinical studies were re-analyzed and a subgroup analysis was performed according to instrument used and according to the severity of disease.

Calculation of Effect Sizes.

MMSE total scores at baseline were used to stage severity of dementia. Study 9605 and MD-12 did not have exactly the same schedule of visits. Day 196 (study 9605) and day 168 (study MD-12)

Table 1. Overall results regarding endpoint 'cognition' in two studies evaluating the treatment of memantine vs. placebo (9605) or memantine plus acetylcholinesterase inhibitor vs. placebo plus acetylcholinesterase inhibitor (MD-12)

Study No.	Analysis	Efficacy total score scale	MMSE subgroup	MEM			PBO			ANCOVA			
				n	mean	SD	n	mean	SD	p value	effect size	95% CI low	95% CI high
9605	LOCF, day 196	SIB	all included	126	−4.05	12.48	126	−9.92	12.48	<0.001***	−0.47	−0.72	−0.22
			10 ≤ MMSE < 15	45	−2.12	13.64	49	−9.79	13.64	0.008**	−0.56	−0.97	−0.14
			MMSE < 10	81	−5.17	11.80	77	−9.95	11.80	0.012*	−0.40	−0.72	−0.09
		MMSE	all included	126	−0.52	2.72	126	−1.14	2.72	0.070	−0.23	−0.47	0.02
			10 ≤ MMSE < 15	45	0.11	3.18	49	−1.32	3.18	0.032*	−0.45	−0.86	−0.04
			MMSE <10	81	−0.88	2.36	77	−1.00	2.36	0.749	−0.05	−0.36	0.26
MD-12	LOCF, day 168	ADAS-cog	all included	212	0.40	5.94	212	1.08	5.94	0.239	−0.11	−0.30	0.08
			10 ≤ MMSE < 15	68	2.37	6.70	58	2.45	6.70	0.946	−0.01	−0.36	0.34
			10 ≤ MMSE < 20	149	0.96	6.25	145	1.97	6.25	0.165	−0.16	−0.39	0.07
			15 ≤ MMSE < 20	81	−0.13	5.69	87	1.56	5.69	0.056	−0.30	−0.60	0.01
		MMSE	all included	214	−0.24	3.04	213	−0.67	3.04	0.145	−0.14	−0.33	0.05
			10 ≤ MMSE < 15	70	−0.95	3.05	59	−1.06	3.05	0.847	−0.04	−0.38	0.31
			10 ≤ MMSE < 20	151	−0.69	2.87	146	−0.88	2.87	0.584	−0.07	−0.29	0.16
			15 ≤ MMSE < 20	81	−0.51	2.75	87	−0.72	2.75	0.622	−0.08	−0.38	0.23

Study 9605 and MD-12 did not have the same schedule of visits. Day 196 (study 9605) and day 168 (study MD-12) were the visits closest to a 6-month observation period. In the MMSE and the SIB, higher scores indicate better performance. In the ADAS-cog, higher scores indicate worse performance. For reasons of readability all analyses were performed so that negative effect sizes indicate that treatment with memantine is favored and positive effect sizes indicate that treatment with placebo is favored.

were the visits closest to a 6-month observation period for the respective study. Since progression of AD is slow, this difference in the timing of endpoints does not have an impact on the comparability of the endpoints. Around 10% of the observations at the last visit are carried forward once in both treatment groups and both studies.

Due to the different scales used in the two studies, it is not possible to pool study data and run an ANCOVA on all patients in both studies. We have used ANCOVA for each study with baseline scores as covariates, and then, as a second step, based on the output from the ANCOVAs, carried out the meta-analysis. The applied ANCOVAs are based on random effects models, analyzed by using the mixed procedure in SAS, and include a test for heterogeneity.

Effect sizes were calculated from the original data. In the calculation of the effect sizes (standardized mean differences), the inverse variances were used as weights. The standard meta-analytic procedures applied yield pooled standard deviations, and consequently confidence intervals around standardized mean differences.

In the MMSE and the SIB higher scores indicate better performance; in the ADAS-cog lower scores indicate better performance. For reasons of readability all analyses were performed so that negative effect sizes indicate that treatment with memantine is favored and positive effect sizes indicate that treatment with placebo is favored.

Results

MMSE and SIB

In a population (study 9605) with moderately severe to severe dementia AD (MMSE <15), the effect sizes at day 196 were −0.23 (95% CI −0.47, 0.02) for the MMSE and −0.47 (95% CI −0.72, −0.22) for the SIB (LOCF method) for patients with moderately severe AD and severe AD, respectively (table 1).

To further analyze this difference we analyzed established subscores of the MMSE and the SIB according to the severity of dementia and according to the cognitive subdomains 'memory', 'orientation', and 'language'. In moderately severe patients (10 ≤ MMSE < 15; msAD) the standard mean difference for 'memory' is calculated with −0.43 (−0.84, −0.02) for the MMSE and with −0.32 (−0.73, 0.08) for the SIB. Likewise, the standard mean difference concerning 'orientation' is calculated with −0.49 (−0.90, −0.08) for the MMSE and −0.28 (−0.69, 0.12) for the SIB. Similarly, the difference is prominent concerning 'language' with −0.20 (−0.60, 0.21) in the MMSE and −0.40 (−0.81, 0.01) for the SIB.

In a subgroup with severe dementia severity (MMSE <10) we analyzed established subscores of the MMSE and

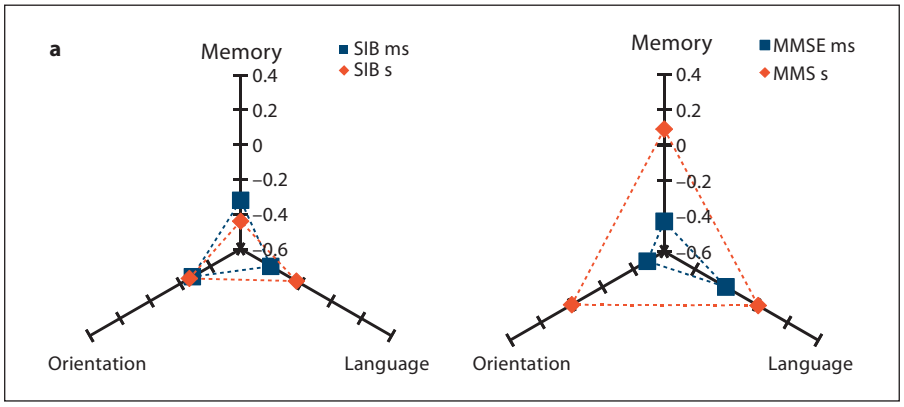

Fig. 1. Fingerprints of subscales of the SIB (**a**) and MMSE (**b**) in moderately severe (ms: 10 ≤ MMSE < 15; blue) and severe (s: MMSE <10; red) dementia. LOCF data represent mean weighted differences between memantine and placebo treatment. Confidence intervals are reported in 'Results'. For reasons of readability, all analyses were performed so that negative effect sizes indicate that treatment with memantine is favored and positive effect sizes indicate that treatment with placebo is favored.

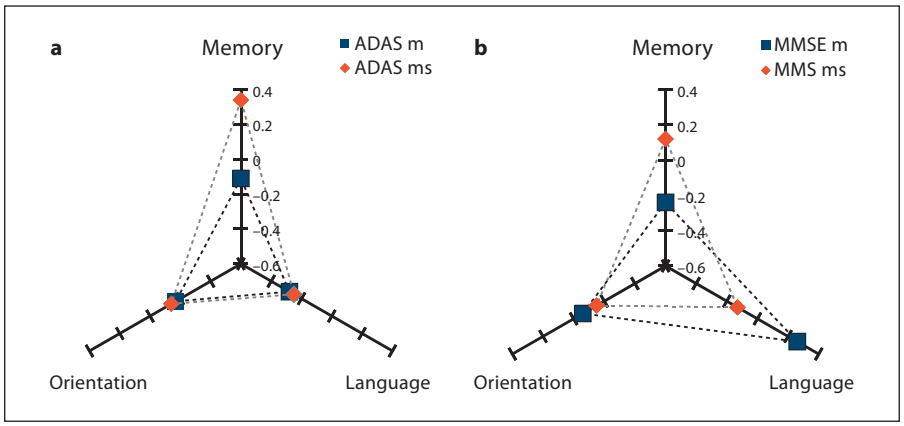

Fig. 2. Fingerprints of subscales of the ADAS (**a**) and the MMSE (**b**) in moderate (m: 15 ≤ MMSE < 20; blue) and moderately severe (ms: 10 ≤ MMSE < 15; red) dementia. LOCF data represent mean weighted differences between memantine plus acetylcholinesterase inhibitor and placebo plus acetylcholinesterase inhibitor treatment. Confidence intervals are reported in 'Results'. For reasons of readability all analyses were performed so that negative effect sizes indicate that treatment with memantine is favored and positive effect sizes indicate that treatment with placebo is favored.

the SIB targeting cognitive subdomains 'memory', 'orientation', and 'language'. The standard mean difference for 'memory' is calculated with 0.09 (–0.22, 0.40) for the MMSE and with –0.44 (–0.76, –0.12) for the SIB. Likewise, the standard mean difference concerning 'orientation' is calculated with 0.00 (–0.31, 0.31) for the MMSE and –0.26 (–0.58, 0.05) for the SIB. The difference is prominent, also, concerning 'language' with 0.01 (–0.30, 0.33) in the MMSE and –0.23 (–0.54, 0.09) for the SIB.

The different fingerprints of efficacy according to cognitive domain, test instrument, and disease severity are presented in figure 1.

ADAS-cog and MMSE

In another population with mild-to-moderate to moderately severe AD the standardized mean weighted differences at day 168 were –0.14 (95% CI –0.33, 0.05) for the MMSE and –0.11 (–0.30, 0.08) for the ADAS-cog (LOCF method) for patients with moderate AD and moderately severe AD, respectively (table 1).

To further analyze this difference, we analyzed established subscores of the ADAS-cog and the MMSE according to the severity of dementia and according to the cognitive subdomains 'memory', 'orientation', and 'language'. In moderate patients (15 ≤ MMSE < 20) the effect size for 'memory' is calculated with –0.11 (–0.41, 0.19) for the ADAS-cog and with –0.24 (–0.55, 0.06) for the MMSE. Likewise, the effect size concerning 'orientation' is calculated with –0.17 (–0.48, 0.13) for the ADAS-cog and –0.06 (–0.36, 0.24) for the MMSE. The difference is most prominent concerning 'language' with –0.28 (–0.58, 0.03) in the ADAS-cog and 0.26 (–0.04, 0.57) for the MMSE.

In a subgroup with moderately severe dementia severity (10 ≤ MMSE < 15), we analyzed established subscores of the ADAS-cog and the MMSE targeting cognitive subdomains 'memory', 'orientation', and 'language'. The effect size for 'memory' is calculated with 0.34 (–0.01, 0.69) for the ADAS-cog and with 0.12 (–0.23, 0.47) for the MMSE. Likewise, the effect size concerning 'orientation' is calculated with –0.14 (–0.49, 0.21) for the ADAS-cog

and –0.15 (–0.50, 0.19) for the MMSE. A difference is also observed concerning 'language' with –0.25 (–0.60, 0.10) in the ADAS-cog and –0.13 (–0.48, 0.22) for the MMSE.

The different fingerprints of efficacy according to cognitive domain, test instrument, and disease severity are presented in figure 2.

Discussion

Dementia is a frequent disorder in the elderly and its prevalence increases with age [4]. The most frequent cause is AD. At onset of AD the medial temporal lobe is affected [12] resulting in episodic memory deficit as the early clinical hallmark [11]. As the disease spreads, other brain regions are affected as well. The parietal cortex mediates functions such as spatial orientation and visuospatial functions [13, 23], the frontal cortex executive functions, planning, attention, and working memory [8, 16, 22]. Spread of AD beyond the temporal lobe thus is characterized in functional terms by accruing deficits of spatial orientation, attention and executive functions as well as working memory and language [11] beyond initial temporal lobe type memory deficits. This can be visualized using advanced imaging methods [9, 10].

Clinical studies use composite scales. Most commonly used are the ADAS-cog, the MMSE [2, 7], and, for more advanced stages of disease, the SIB. Few clinical studies use these instruments in parallel to target the same endpoint in patients with AD. To analyze how interpretation is subject to the influence of disease severity and instruments used, we reanalyzed two clinical studies with memantine in patients with AD using more than one scale targeting the same endpoint 'cognition'. Despite several clinical studies demonstrating the efficacy of memantine in patients with AD in a variety of settings [5, 19, 20, 25, 26] several meta-analyses considered the therapeutic efficacy on 'cognition' to be small [1, 14]. The analysis in the current manuscript demonstrates that rather than only performing meta-analyses over the whole spectrum of disease severity and clinical scales, an itemized analysis with regard to severity of disease and instrument used is also necessary.

Cognitive scales mingle the results of several cognitive functions into one composite score. While any of the assessed symptoms might be present at one time point or the other during the course of an individual's disease they will not be present all at once at any given stage of disease. Moreover, the dynamic range for observation of change is not the whole range of the scale but a small range centered around the observed score. Unfortunately, the sensitivity to change of these scores is not linear over the course of disease [2, 15]. It already has been reported that subgroups of patients may show significant differences in one test compared to another, namely in the MMSE compared to the SIB [17].

One of the most common methods to combine effect sizes from different studies is the standardized mean difference method. The average effect size is calculated and the weights are the inverse variances of the means from each study. The idea behind this procedure is that studies with the least variability will receive the highest weighting in determining the overall result. However, this assumes that the least variability results from the largest sample size rather than from insensitivity of scales in different stages of disease. The present analysis demonstrates that standardized mean differences in 'cognition' result from use of different scales rather than random variation in study populations or their response to treatment. Even more so, if floor or ceiling effects are present which would be the case in applying the ADAS-cog to severely affected individuals, the results of applying weighted mean difference would be distorted even more.

Even if in the final analysis a random effects model is applied which in contrast to a fixed effects model does allow random study-to-study variability for underlying true effect sizes this only accounts for variability of effect size resulting from sample size and potentially stage of disease it does not account for the true variability resulting from application of tests with differential response characteristics in the domains of analysis.

In summary, beyond interstudy variance, effect sizes for treatment with antidementia drugs are subject to disease stage, instruments used, and interaction thereof. Therefore, clinical interpretation is necessary to appraise therapeutic efficacy in clinical studies and meta-analyses thereof when patients with different severity are included or different instruments are used. Alternatively, severity-adapted endpoints should be used for appraisal and meta-analysis of therapeutic efficacy.

Disclosure Statement

M.W.R. has received study grants, speaker fees, and has participated in advisory boards from AstraZeneca, Eisai, Elan, Janssen, Lundbeck, Merz, Novartis, Pfizer and other funding from organizations including the German Federal Ministry of Health, the German Federal Ministry of Science and Education, and the Deutsche Forschungsgemeinschaft. W.J. and O.M.L. are employees of Lundbeck.

References

1 Areosa SA, Sherriff F: Memantine for dementia. Cochrane Database Syst Rev 2003;CD003154.

2 Ashford JW, Kolm P, Colliver JA, Bekian C, Hsu LN: Alzheimer patient evaluation and the mini-mental state: item characteristic curve analysis. J Gerontol 1989;44:139–146.

3 Benge JF, Balsis S, Geraci L, Massman PJ, Doody RS: How well do the ADAS-cog and its subscales measure cognitive dysfunction in Alzheimer's disease? Dement Geriatr Cogn Disord 2009;28:63–69.

4 Erkinjuntti T, Ostbye T, Steenhuis R, Hachinski V: The effect of different diagnostic criteria on the prevalence of dementia. N Engl J Med 1997;337:1667–1674.

5 Feldman HH, Schmitt FA, Olin JT: Activities of daily living in moderate-to-severe Alzheimer disease: an analysis of the treatment effects of memantine in patients receiving stable donepezil treatment. Alzheimer Dis Assoc Disord 2006;20:263–268.

6 Folstein MF, Folstein SE, McHugh PR: 'Mini-mental state': a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–198.

7 Folstein MF, Robins LN, Helzer JE: The Mini-Mental State Examination. Arch Gen Psychiatry 1983;40:812.

8 Godefroy O, Cabaret M, Petit-Chenal V, Pruvo JP, Rousseaux M: Control functions of the frontal lobes: modularity of the central-supervisory system? Cortex 1999;35:1–20.

9 Gron G, Bittner D, Schmitz B, Wunderlich AP, Riepe MW: Subjective memory complaints: objective neural markers in patients with Alzheimer's disease and major depressive disorder. Ann Neurol 2002;51:491–498.

10 Gron G, Riepe MW: A neural basis of the cognitive continuum in episodic memory from health to Alzheimer's disease. Am J Geriatr Psychiatry 2004;12:648–652.

11 Hodges JR: Memory in the dementias; in Tulving E, Craik FIM (eds): The Oxford Handbook of Memory. Oxford, Oxford University Press, 2000, pp 441–459.

12 Hyman BT, Van Horsen GW, Damasio AR, Barnes CL: Alzheimer's disease: cell-specific pathology isolates the hippocampal formation. Science 1984;225:1168–1170.

13 Marshall JC, Fink GR: Spatial cognition: where we were and where we are. Neuroimage 2001;14:S2–S7.

14 McShane R, Areosa SA, Minakaran N: Memantine for dementia. Cochrane Database Syst Rev 2006;CD003154

15 Mendiondo MS, Ashford JW, Kryscio RJ, Schmitt FA: Modelling mini mental state examination changes in Alzheimer's disease. Stat Med 2000;19:1607–1616.

16 Nagahama Y, Okada T, Katsumi Y, Hayashi T, Yamauchi H, Oyanagi C, Konishi J, Fukuyama H, Shibasaki H: Dissociable mechanisms of attentional control within the human prefrontal cortex. Cereb Cortex 2001;11:85–92.

17 Panisset M, Roudier M, Saxton J, Boller F: Severe impairment battery: a neuropsychological test for severely demented patients. Arch Neurol 1994;51:41–45.

18 Porsteinsson AP, Grossberg GT, Mintzer J, Olin JT: Memantine treatment in patients with mild to moderate Alzheimer's disease already receiving a cholinesterase inhibitor: a randomized, double-blind, placebo-controlled trial. Curr Alzheimer Res 2008;5:83–89.

19 Reisberg B, Doody R, Stoffler A, Schmitt F, Ferris S, Mobius HJ: Memantine in moderate-to-severe Alzheimer's disease. N Engl J Med 2003;348:1333–1341.

20 Rive B, Vercelletto M, Damier FD, Cochran J, Francois C: Memantine enhances autonomy in moderate to severe Alzheimer's disease. Int J Geriatr Psychiatry 2004;19:458–464.

21 Rosen WG, Mohs RC, Davis KL: A new rating scale for Alzheimer's disease. Am J Psychiatry 1984;141:1356–1364.

22 Rowe JB, Toni I, Josephs O, Frackowiak RS, Passingham RE: The prefrontal cortex: response selection or maintenance within working memory? Science 2000;288:1656–1660.

23 Save E, Poucet B: Hippocampal-parietal cortical interactions in spatial cognition. Hippocampus 2000;10:491–499.

24 Saxton J, Swihart AA: Neuropsychological assessment of the severely impaired elderly patient. Clin Geriatr Med 1989;5:531–543.

25 Tariot PN, Farlow MR, Grossberg GT, Graham SM, McDonald S, Gergel I: Memantine treatment in patients with moderate to severe Alzheimer disease already receiving donepezil: a randomized controlled trial. JAMA 2004;291:317–324.

26 Winblad B, Poritis N: 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 1999;14:135–146.