INTERNATIONAL JOURNAL OF GERIATRIC PSYCHIATRY
Int J Geriatr Psychiatry 2004; **19**: 458–464.
Published online in Wiley InterScience (www.interscience.wiley.com). **DOI**: 10.1002/gps.1112

Memantine enhances autonomy in moderate to severe Alzheimer's disease

Benoît Rive[1]*, Martine Vercelletto[2], Florence Delamarre Damier[3], John Cochran[4] and Clément François[4]

[1]*Altipharm SA, Paris, France*
[2]*Memory Centre, Department of Neurology, R and G Laënnec Hospital, Nantes, France*
[3]*ITG Consulting Group, Paris, France*
[4]*H. Lundbeck A/S, Paris, France*

SUMMARY

Background Alzheimer's disease (AD) is the leading cause of dementia and its course renders patients functionally disabled. Memantine is the first drug to demonstrate a clinical benefit in the treatment of patients with moderately-severe to severe AD.
Objectives Our objective was to illustrate the benefits of memantine on functional disability.
Methods We classified 252 patients from a randomised 28-week clinical trial of memantine vs placebo according to their Activities of Daily Living capabilities measured by the ADCS-ADLsev scale. The scale was divided into two sub-scores: basic and instrumental. The relevance of this classification was validated by comparing clinical and socio-demographic parameters between the different autonomy classes (autonomous and dependent). The effect of memantine was estimated by using a logistic regression model on the autonomy status of patients at week 28, controlling for confounding factors (Observed Cases analysis).
Results Our results showed that dependent patients ($n = 106$) had significantly longer disease duration, poorer cognition, greater severity, more behavioural alterations and higher total societal costs compared with autonomous patients ($n = 146$). When controlling for autonomy and severity at baseline, memantine-treated patients were three times more likely [Odds Ratio (OR) = 3.03; 95% Confidence Intervals (CI) = (1.38, 6.66)] to remain autonomous after 28 weeks. Analysis of the Treated Per Protocol set and the use of Last Observation Carried Forward analyses confirmed this finding.
Conclusions Memantine enhances autonomy in patients with moderately-severe to severe AD by increasing the probability of their remaining autonomous, therefore delaying transition to the dependent stage. Copyright © 2004 John Wiley & Sons, Ltd.

KEY WORDS — Alzheimer's disease; Activities of Daily Living; autonomy; memantine

INTRODUCTION

Alzheimer's disease (AD) is the leading cause of dementia and is characterised by the progressive deterioration of cognition, behaviour, mood and learning abilities. Its course renders patients functionally disabled; a condition that is defined as 'any restriction or inability to perform an activity in the manner or within the range considered normal for a human being' (World Health Organisation, 1980). From both clinical and regulatory perspectives, measuring the level of a patient's functional disability is becoming a primary criterion for assessing the benefit of any AD drug.

Memantine is a voltage-dependent, moderate-affinity, 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 *et al.*, 2000). It is the first molecule to demonstrate a clinical benefit

*Correspondence to: Dr B. Rive, Altipharm SA, 15 rue du Louvre, 75001 Paris, France. Tel: +33 1 53 67 73 87. Fax: +33 1 53 67 42 67. E-mail: benoit_rive@hotmail.com

Contract/grant sponsors: Merz Pharmaceuticals GmbH; H. Lundbeck A/S.

Received 1 October 2003
Accepted 26 January 2004

in the treatment of patients with moderately-severe to severe AD (Winblad *et al.*, 1999; Reisberg *et al.*, 2003).

Currently, functional levels are measured by Activities of Daily Living (ADL) scales that provide only quantitative scores that may be vulnerable to different interpretations. Additionally, differences in scores arise when comparing treatment arms or consecutive assessments. This further complicates interpretation. Because there is no consensus, no specific ADL scale is recommended (Gauthier *et al.*, 1997). Most scales assess various activities associated with daily living. We can make a distinction between the activities as they relate to self-care [Basic Activities of Daily Living (B-ADL)] as well as environmental adaptation [Instrumental Activities of Daily Living (I-ADL)]. B-ADLs are simple activities (eating, dressing one self, transferring, bathing), whereas I-ADLs are more complex activities (using the telephone, preparing a meal, doing the washing).

In order to simplify the interpretation of patient evolution through the course of the disease, Kurz *et al.* (2003) recently developed a new qualitative evaluation of AD patients based on their autonomy evaluated from ADL scores. This classification allows evaluation of AD patients over the continuum of the disease. The progression of the disease can be clearly measured by the transitions between different states, instead of by differences in quantitative scores alone.

We applied this methodology to evaluate the treatment effect of memantine on functional disability in a double-blind randomised clinical trial (Reisberg *et al.*, 2003).

PARTICIPANTS AND METHODS

The study population consisted of 252 patients who scored between 3 and 14 (inclusive) on the Mini-Mental State Examination (MMSE) (Folstein *et al.*, 1975) scale at baseline and was derived from a randomised double-blind clinical trial that studied the efficacy and long-term tolerability of memantine 20 mg daily vs placebo for a period of 28 weeks (Reisberg *et al.*, 2003). This study also collected socio-demographic, economic and patient AD history data.

Patient classification

Activities of Daily Living (ADL) were assessed in the clinical study using the Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory (ADCS-ADL) (Galasko *et al.*, 1997) modified for more severe dementia (ADCS-ADLsev) (Galasko *et al.*, 2000). Using the nearest centroid sorting algorithm (SAS PROC FASTCLUS, SAS Institute Inc., Cary, NC), all patients were classified according to their basic and instrumental ADL (B-ADL and I-ADL respectively) capabilities. This followed the approach used by Kurz *et al.* (2003) to simplify the interpretation of a patient's functional evolution. Basic and instrumental scores were constructed from the ADCS-ADLsev scale. B-ADLs were calculated as the sum of all basic activities (such as eating, walking, bathing, grooming, dressing and toileting) contained in the full scale. I-ADLs were calculated as the sum of all the instrumental activities contained in the ADCS-ADLsev scale. The scores for all patients were standardised (mean = 0; SD = 1) to attribute the same importance to the two scores. Using these two scores, an automatic patient classification was performed. The classification algorithm first computed the cluster seeds and then iteratively assigned each patient to the cluster with the nearest seed. This classification method provided an explicit formulation of an autonomy criterion as the set of all right bisectors between two cluster seeds. For each new patient, each right bisector between two cluster seeds determined to which cluster the patient was nearest. By comparing the information for all right bisectors, the autonomy status of each patient was determined.

The number of clusters was determined by maximising the pseudo F statistic, limiting the number of clusters to five in order to avoid interpretation problems.

External validity of the classification

The classification scheme was validated by comparing baseline characteristics of the patients between the different clusters, assuming that a relevant autonomy definition would influence these domains. These included patient age, gender, disease duration and onset, as well as clinical assessments, costs and caregiver time.

Clinical assessments covered several aspects of the disease. Cognitive function was measured using the MMSE and Severe Impairment Battery (SIB) (Panisset *et al.*, 1994; Schmitt *et al.*, 1997) scales. Behavioural symptoms were assessed using the Neuropsychiatric Inventory (NPI) (Cummings *et al.*, 1994) and the degree of severity was determined using the Functional Assessment Staging scale (FAST) (Sclan *et al.*, 1992) and the Global Deterioration Scale (GDS) (Reisberg *et al.*, 1982). The Clinician's Interview Based Impression of Change Plus

Caregiver Input (CIBIC-plus) (Reisberg *et al.*, 1997) scale was used as a primary efficacy outcome in the clinical trial. However, since this scale is designed to measure the patient's evolution, it could not be used to compare the different clusters.

The Resource Utilisation in Dementia (RUD) (Wimo *et al.*, 1998) questionnaire assessed resource use. Unit costs corresponding to each resource were taken from the study conducted by Wimo *et al.* (2003) and are expressed in $US (1999). The RUD questionnaire also included a part that measured the mean monthly time spent by the caregiver in helping/assisting the patient.

Cluster differences were verified using a Wilcoxon-Mann–Whitney test for quantitative data because most of the scores were not normally distributed as required by the Student test. A chi-square test was used for qualitative data. The basic level of significance of both tests was 5% (bilateral) adjusted by the Bonferoni method according to the number of tests required to compare each pair of clusters.

Evaluation of the impact of memantine on patient autonomy level

Basic and instrumental scores at the end of the double-blind period were computed according to the Observed Cases (OC) method. Based on these scores and by applying our criterion, the autonomy level of patients at week 28 was determined. The effect of memantine after 28 weeks of treatment on the probability of a patient being in a particular autonomy level was estimated by logistic regression. Initially, the following covariates were included: B-ADL, I-ADL scores and severity (moderately severe: MMSE $\geq$10 or severe: MMSE $<$10) at baseline, study treatment (memantine 20 mg daily or placebo), age, gender, duration and early onset (before the age of 65 years) of the disease. We used a backward elimination process, retaining variables at the $p = 0.05$ level to specify the final model. The backward elimination process allowed the retention of only significant explanatory covariates in the model and the removal of covariates that added noise. The Hosmer and Lemeshow goodness-of-fit statistic was used to assess the model fit. The global predictive performance of the model was estimated by using the c-statistic (area under the Receiver Operating Characteristic curve). Additional analyses using the Treated Per Protocol (TPP) population and the Last Observation Carried Forward (LOCF) method for the two ADL scores were conducted in order to confirm the robustness of the results. Five patients (two in the memantine group and three in the placebo group) had no post-baseline assessment for the ADCS-ADLsev scale and were therefore excluded from these analyses.

RESULTS

The maximization of the pseudo F statistic enabled patients to be classified into only two clusters. (Table 1) Out of the 252 patients included in the trial, a total of 106 patients were allocated to Cluster 1 and 146 patients to Cluster 2. By definition, the cluster with the lowest scores (Cluster 1) contained the dependent patients and Cluster 2 the autonomous patients (Table 2 and Figure 1; note that B-ADL scores varied between 1 and 19, while I-ADL scores varied between 1 and 31).

Since the classification process resulted in two classes, the autonomy criterion consisted of only

Table 1. Number of clusters and pseudo F statistic

Number of Clusters	Pseudo F Statistic
2	313
3	281
4	257
5	258

Table 2. Basic and Instrumental ADL scores—per cluster

	Autonomous $n = 106$	Dependent $n = 146$
Basic score		
Mean (SD)	14.4 (2.5)	8.4 (3.3)
Range	8–19	1–15
Instrumental score		
Mean (SD)	19.7 (4.6)	9.08 (4.3)
Range	10–31	1–18

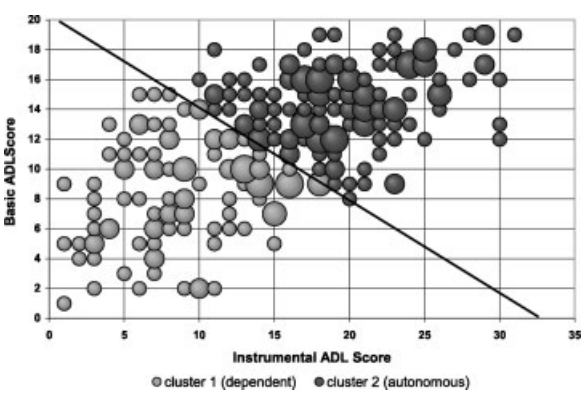

Figure 1. Bubble diagram of I-ADL score vs B-ADL score and identification of clusters (the area of bubbles is proportional to the number of patients)

one equation (right bisector between the seeds of the two clusters). If I-ADL + 1.6 × B-ADL > 32.4, then the patient was autonomous otherwise the patient was dependent.

No significant differences between autonomous and dependent patients were found for gender (chi-square $p = 0.134$) or age (Wilcoxon-Mann–Whitney $p = 0.106$). Sixty-two percent of the dependent patients were female compared to 71% of the autonomous patients. Dependent patients (mean age = 77.9, SD = 7.4) were slightly older than autonomous patients (mean age = 75.9, SD = 8.4).

Duration of illness was significantly higher (Wilcoxon-Mann–Whitney $p = 0.033$) for dependent patients (mean = 5.8 years, SD = 3.4) than for autonomous patients (mean = 5.1 years, SD = 3.9). Early onset of the disease (before age 65) was not significantly different (chi-square $p = 0.547$) between autonomous (24.0% with early onset) and dependent patients (20.8%).

Statistically significant differences appeared between autonomous and dependent patients on the MMSE, SIB, FAST, GDS and NPI scales at baseline (Table 3). All differences were in favour of autonomous patients thereby indicating that these patients have significantly less cognitive, functional and behavioural disturbances than dependent patients.

Caregiver time and societal costs were significantly greater for dependent patients than for autonomous patients (Table 4). Moreover, there were a higher proportion of institutionalised patients in the dependent group (10.5%) than in the autonomous group (5.7%). However, this difference did not reach statistical significance.

Table 3. The influence of autonomy on cognitive, behavioural, and functional scales at baseline

	Autonomous Mean (SD)	Dependent Mean (SD)	Wilcoxon-Mann–Whitney p
MMSE	8.9 (3.6)	6.6 (3.2)	<0.001
SIB	75.8 (16.6)	55.1 (22.3)	<0.001
FAST*	2.2 (1.0)	3.7 (1.3)	<0.001
GDS	5.4 (0.5)	5.8 (0.4)	<0.001
NPI	17.4 (13.0)	25.4 (17.6)	<0.001

*The FAST scores were calculated by enumerating the FAST stages and substages as follows: stage 3 (a score of −2) through 5 (0) and substage 6a (1) through substage 7f (11).

Table 4. The influence of autonomy upon resource use at baseline

	Autonomous Mean (SD)	Dependent Mean (SD)	Wilcoxon-Mann–Whitney p
Total caregiver time (Hours per month)	377 (264)	533(228)	<0.001
Total societal cost (Monthly cost in 1999 USD)	6937 (4769)	9733 (4538)	<0.001

Table 5. Odds ratio and confidence limits of the effects of the logistic regression model (OC analysis)

Covariate	Odds ratio	Confidence intervals (95%)	Wald p-value
Treatment: memantine vs placebo	3.03	1.38–6.66	0.006
Severity: moderately-severe vs severe	2.22	1.06–4.65	0.035

As the automatic classification consistently separates autonomous from dependent patients, we applied this criterion to obtain the autonomy status of patients at the end of the study (28 weeks).

After adjustment for B-ADL and I-ADL scores at baseline, only treatment and baseline severity had a significant impact on patient autonomy at week 28. Odds ratios (OR) and the corresponding 95% confidence intervals (CI) of these effects are presented in Table 5. When controlling for B-ADL and I-ADL scores and severity at baseline, a patient treated with memantine was more than three times as likely [OR = 3.03; 95%CI = (1.38, 6.66)] to be autonomous after 6 months.

The goodness-of-fit test revealed no significant inadequacy between the model and the data ($p = 0.426$) and the model showed accurate predictive characteristics (C-statistic = 0.884).

Additional analyses using the TPP population (78 placebo patients and 93 memantine patients) or the LOCF computation method (on the 247 patients having at least one post-baseline ADCS-ADLsev assessment) showed similar results. In both cases memantine had a significant benefit on patient autonomy at week 28.

Several differences with the OC analysis were noticed. The two confirmatory analyses revealed that severity at baseline had no significant effect on autonomy at week 28. It was therefore eliminated from the logistic model during the backward selection process. The Wald chi-square of severity at baseline at its elimination from the logistic model was 0.188 for the TPP population and 0.060 for the LOCF computation method. Finally, early onset of the disease significantly decreased the odds of being autonomous at week 28 when considering the TPP population. Results of the logistic regression on the TPP population are presented in Table 6, and results using the LOCF method are presented in Table 7.

Table 6. Odds ratio and confidence limits of the logistic regression model (TPP)

Covariate	Odds ratio	Confidence intervals (95%)	Wald *p*-value
Treatment: memantine versus placebo	2.88	1.15–7.23	0.024
Onset: >65 years old vs ≤65	3.24	1.19–8.86	0.022

Table 7. Odds ratio and confidence limits of the logistic regression model (LOCF)

Covariate	Odds ratio	Confidence intervals (95%)	Wald *p*-value
Treatment: memantine vs placebo	2.31	1.12–4.76	0.023

Table 8. Characteristics of the logistic regression models

	Goodness-of-fit test	C-statistic
OC	0.426	0.884
TPP	0.964	0.896
LOCF	0.357	0.891

The characteristics of the two models are presented in Table 8. In both cases, no significant inadequacy between the model and the data appeared and the models showed accurate predictive characteristics.

DISCUSSION

The benefit evaluation of a drug for the treatment of AD is particularly difficult to assess when applied to severely ill patients. The automatic classification process led to a clearer understanding of a patient's functional evolution by converting quantitative ADL scores into either dependent or autonomous classes. This revealed that memantine increases the odds of moderately-severe to severe AD patients being autonomous after 28 weeks, thus delaying transition to the dependent stage.

The reliability of our findings was ensured by both the design of the study (a randomised, double-blind, placebo-controlled clinical trial) (Reisberg *et al.*, 2003) and the method used to estimate the benefit of memantine. The benefit was evaluated by a logistic regression model controlling for other factors identified as having an impact on autonomy. The model correctly fitted the observed data and showed accurate predictive characteristics. Furthermore, the robustness of the results was reconfirmed by TPP and LOCF analyses. Since AD is a neurodegenerative disease, the LOCF method artificially overestimates the clinical state of dropout patients by simulating stability where deterioration is more likely to occur. As such, it gives an advantage to the treatment arm with the higher dropout rate. As shown in the Reisberg *et al.* (2003) study, the placebo dropout rate (33%) was 10% higher than the memantine dropout rate (23%). This additional analysis gave conservative results, and the fact that memantine showed a significant effect on autonomy (despite the difference in dropout rates between the two treatment groups) further strengthens the reliability of our findings.

Our conception of autonomy could be appraised from wider perspectives; for instance, the fact that we used only ADL measurements could be seen as a possible restriction to our definition. Nevertheless, we showed that the autonomy criterion is associated with all other clinical measures, whether they concern the level of severity or the cognitive, neuropsychiatric or functional domains. Consequently, we provide an additional and perhaps more balanced appraisal of a patient's clinical state, which is correlated with all clinical dimensions of the disease. The relevance of ADL measures has been clearly established and the Committee for Proprietary Medicinal Products (CPMP) guidance on new medicines for the treatment of AD (Committee for Proprietary Medicinal Products, 1997) recommends that significant improvement on functional and global endpoints can be considered as primary evidence of clinically relevant symptomatic improvement.

No Quality of Life (QoL) assessment was recorded during the course of the clinical trial, so no correlation between the patient's autonomy and their QoL or the QoL of their caregiver could be established. However, no consensus exists as to the choice of a scale for assessing the QoL of patients or their caregivers (Salek *et al.*, 1998). Moreover, the time spent by the caregiver in assisting/helping the patient with their daily activities could be considered as a proxy measurement for caregiver QoL. Dependent patients required a significantly greater amount of caregiver time than autonomous patients. This fact alone tends to show that caregivers of autonomous patients may have a better QoL than caregivers of dependent patients.

Furthermore, dependent patients incurred higher costs than autonomous patients. In addition to clinical appraisals, autonomy—as we defined it—appears as a means to identify the socioeconomic aspects of care.

Most of these findings are consistent with those found by Kurz *et al.* (2003). The only discrepancies concern age and institutionalisation, which were associated with autonomy level in the Kurz *et al.* study and revealed only trends toward association in the present study. However, since our study population was taken from a clinical trial, and as such is more restricted than the population as a whole, it was far more homogenous than the Kurz *et al.* population (e.g. only AD vs all dementias, moderately-severe to severe patients vs all severities, etc.). Moreover, very few patients were institutionalised in both autonomy groups, making it harder to detect any difference between them.

The case of borderline patients may also raise an issue. Actually, two patients can be assigned to different autonomy groups even if they present similar B-ADL and I-ADL scores supposing they are close enough to the borderline separating the two groups. However, despite the natural loss of information resulting from the classification process (not possible to determine exactly the basic and instrumental ADL scores when only the autonomy level of a patient is known), as in the Kurz *et al.* study, we obtained a relevant definition of autonomy. This definition appears to have a central role because it is connected to the major dimensions of the disease: severity, cognitive, functional, behaviour and costs and burden of care. A posteriori, classification is justified even if assigning borderline patients to one of the two groups may appear arbitrary.

In conclusion, by enhancing autonomy, memantine may reduce costs and decrease the overall burden of care. Wimo *et al.* (2003) have previously shown that memantine decreased the costs and burden of care. It is possible that the effect of memantine on autonomy can partially explain these findings.

Previous cost-effectiveness studies for AD treatments have used the amount of time expended until a patient transits to the severe stage as the measure of efficacy (Stewart *et al.*, 1998; Neumann *et al.*, 1999). However, this method is not applicable for patients already in the severe stage; those patients for whom memantine is indicated. Future cost-effectiveness studies should consider using the length of time spent in the autonomous state as a global measure of overall treatment efficacy.

ACKNOWLEDGEMENT

This study was funded by Merz Pharmaceuticals GmbH and H. Lundbeck A/S.

REFERENCES

Committee for Proprietary Medicinal Products. 1997. Note for guidance on medicinal products in the treatment of Alzheimer's disease. CPMP/EWP/553/95. Ref Type: Bill/Resolution.

Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J. 1994. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. *Neurology* **44**: 2308–2314.

Danysz W, Parsons CG, Möbius HJ, Stöffler A, Quack G. 2000. Neuroprotective and symptomalogical action of memantine relevant for Alzheimer's disease—a unified glutamatergic hypothesis on the mechanism of action. *Neurotoxicity Res* **2**: 85–98.

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

Galasko D, Bennett D, Sano M, *et al.* 1997. An inventory to assess activities of daily living for clinical trials in Alzheimer's disease: the Alzheimer's Disease Cooperative Study. *Alzheimer Dis Assoc Disord* **11**(Suppl. 2): S33–S39.

Galasko DR, Schmitt FA, Jin S, *et al.* 2000. Detailed assessment of cognition and activities of daily living in moderate to severe Alzheimer's disease. *Neurobiol Aging* **21**(Suppl. 1): S168 [abstract].

Gauthier S, Bodick N, Erzigkeit E, *et al.* 1997. Activities of daily living as an outcome measure in clinical trials of dementia drugs: position paper from the International Working Group on Harmonization of Dementia Drug Guidelines. *Alzheimer Dis Assoc Disord* **11**(Suppl. 3): 6–7.

Kurz X, Scuvee-Moreau J, Rive B, Dresse A. 2003. A new approach to the qualitative evaluation of functional disability in dementia. *Int J Geriatr Psychiatry* **18**: 1050–1055.

Neumann PJ, Hermann RC, Kuntz KM, *et al.* 1999. Cost-effectiveness of donepezil in the treatment of mild or moderate Alzheimer's disease. *Neurology* **52**(6): 1138–1145.

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

Reisberg B, Ferris SH, de Leon MJ, Crook T. 1982. The Global Deterioration Scale for assessment of primary degenerative dementia. *Am J Psychiatry* **139**: 1136–1139.

Reisberg B, Schneider L, Doody R, *et al.* 1997. Clinical global measures of dementia: position paper from the International Working Group on Harmonization of Dementia Drug Guidelines. *Alzheimer Dis Assoc Disord* **11**(Suppl. 3): 8–18.

Reisberg B, Doody R, Stoffler A, Schmitt F, Ferris S, Mobius HJ, Memantine Study Group. 2003. Memantine in moderate-to-severe Alzheimer's disease. *N Engl J Med* **348**(14): 1333–1341.

Salek SS, Walker MD, Bayer AJ. 1998. A review of quality of life in Alzheimer's disease—Part 2: issues in assessing drug effects. *Pharmacoeconom* **14**(6): 613–627.

Schmitt FA, Ashford W, Ernesto C, *et al.* 1997. The Severe Impairment Battery: concurrent validity and assessment of longitudinal change in Alzheimer's disease: the Alzheimer's Disease Cooperative Study. *Alzheimer Dis Assoc Disord* **11**(Suppl. 2): S51–S56.

Sclan SG, Reisberg B. 1992. Functional assessment staging (FAST) in Alzheimer's disease: reliability, validity, and ordinality. *Int Psychogeriatr* **4**(Suppl. 1): 55–69.

Stewart A, Phillips R, Dempsey G. 1998. Pharmacotherapy for people with Alzheimer's disease: a Markov-cycle evaluation of five years' therapy using donepezil. *Int J Geriatr Psychiatry* **13**(7): 445–453.

Wimo A, Wetterholm AL, Mastey V, Winblad B. 1998. Evaluation of the healthcare resource utilization and caregiver time in

anti-dementia drug trials. In *Health Economics of Dementia*, Wimo A, Jönsson B, Karlsson G, Winblad B (eds). John Wiley: Chichester; 465–499.

Wimo A, Winblad B, Stoffler A, Wirth Y, Mobius HJ. 2003. Resource utilisation and cost analysis of memantine in patients with moderate 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.

World Health Organisation. 1980. International Classification of Impairment, Disabilities and Handicaps. World Health Organisation: Geneva.

