Original Research Article

Dementia and Geriatric Cognitive Disorders

Dement Geriatr Cogn Disord 2011;32:267–272
DOI: 10.1159/000334991

Accepted: November 7, 2011
Published online: January 9, 2012

Memantine in Everyday Clinical Practice: A Comparison of Studies in Germany and Greece

H. Förstl[a] S.S. Stamouli[c] W. Janetzky[b] A. Galanopoulos[d] C. Karageorgiou[e] M. Tzanakaki[f]

[a]Department of Psychiatry and Psychotherapy, Technische Universität München, Munich, and [b]Lundbeck GmbH, Hamburg, Germany; [c]Psychiatric Hospital 'Eginiteion', [d]Lundbeck Hellas A.E. and [e]General Hospital 'G. Gennimatas', Athens, and [f]General Hospital 'Agios Georgios', Chania, Greece

Key Words
Alzheimer's disease · Non-interventional study · Memantine · Cognition · Activities of daily living

Abstract
Background/Aims: Results from German and Greek non-interventional studies were compared to investigate possible differences concerning efficacy, tolerability and compliance between both countries. ***Methods:*** In two open-label, multicentre, non-interventional studies, 4,305 patients with mild to severe Alzheimer's disease (AD) were treated with daily doses of 20 mg memantine for 6 months. Efficacy was assessed using the Mini-Mental State Examination (MMSE) and instrumental activities of daily living (IADL) scales. Safety and tolerability were recorded. ***Results:*** After 6 months, the patients showed an improvement of their cognitive performance by 2 MMSE points compared to baseline ($p < 0.001$). MMSE values were improved in 67.4% of the patients, while 15.1% remained stable, and MMSE deteriorated in 17.5% only. The ability to perform IADL increased, as is indicated by lower values (baseline: 70.5; after 6 months: 66.6 points). Improvement of cognition and IADL was nearly identical in both countries. Treatment discontinuation was significantly more frequent in the Greek population, mainly due to non-adherence (9.4% of the safety population). 345 adverse events were recorded in 245 patients (6.3%), and they were significantly associated with country and age. ***Conclusion:*** The results correspond to those of clinical trials and support the efficacy and good tolerability of memantine in a realistic setting. Differences between the countries were observed regarding the baseline characteristics of patients (more female, older and more severe patients in Germany as well as less pretreatment with cholinesterase inhibitors) and regarding premature discontinuation and reported adverse drug reactions, which were both higher in Greece.

Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder associated with an almost relentless deterioration of cognitive function and activities of daily living [1]. AD affects the lives of patients and carers and represents a major ethical and economical challenge for modern, aging societies. However, care and care-related costs are still provided by the family, rather than by the health insurance system [2, 3].

KARGER

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

1420–8008/11/0324–0267$38.00/0

Accessible online at:
www.karger.com/dem

Prof. Dr. H. Förstl
Klinik und Poliklinik für Psychiatrie und Psychotherapie
Ismaninger Strasse 22
DE–81675 München (Germany)
Tel. +49 89 4140 4200, E-Mail hans.foerstl@lrz.tum.de

New approaches to target the suspected culprits, i.e. β-amyloid and tau pathology, did not yield any early clinical benefit. Therefore, the symptomatic effects of the substances available today have received renewed recognition and will retain some importance in the forthcoming years [4]. Current pharmacological treatment options for AD include cholinesterase inhibitors (ChEIs) for mild to moderately severe AD in Europe, and memantine for the treatment of moderate to severe AD. Based on the published evidence, European guidelines and institutions [5–8] recommend both ChEIs and memantine for the treatment of AD.

Published meta-analyses [9, 10] of randomized placebo-controlled double-blind trials (RCTs) have shown that memantine has statistically significant effects on cognition, activities of daily living and clinical global function together with a favourable safety and tolerability profile [10]. Memantine significantly delays clinical worsening in these key domains of AD compared to placebo [11].

RCTs are the standard for the evaluation of a drug's efficacy and safety, but further data on efficacy and tolerability need to be collected in non-interventional studies (NISs) using more realistic settings, ideally including the environment in which the substances will be used. Therefore, several NISs with memantine were performed in different countries. It is the aim of the present study to analyse similarities and differences between German and Greek NIS results [12, 13].

Methods

Complete databases to allow for comparative analyses were made available by two open-label, multicentre NISs in Greece and Germany, sponsored by Lundbeck, in which patients with AD were treated daily with 20 mg memantine for 6 months [12, 13]. Participating physicians were primarily working in private practices (general practitioners, neurologists, psychiatrists).

Patient Population

For the selection of patients to be included in the NISs, no specific requirements were in place apart from the diagnosis of AD made in accordance with clinical criteria. The exclusion criterion was the participation in another clinical trial at the same time, thus avoiding any possible interaction between memantine and a trial drug. Otherwise the contraindications and safety recommendations listed in the Summary of Product Characteristics had to be considered.

Outcome Measures

Baseline assessment at the time of inclusion into the study consisted of demographic data and information on previously prescribed antidementia drugs. Patients were examined at baseline, and after 3 and 6 months. Cognition was assessed by applying the Mini-Mental State Examination (MMSE), instrumental activities of daily living (IADL) scale (Greece, 8 items: ability to use the telephone, shopping, food preparation, housekeeping, laundry, mode of transportation, responsibility for own medication, ability to handle finances [14]) or the IADL subscale as part of the Nurses' Observation Scale for Geriatric Patients (Germany, 5 items: follows favourite radio or TV programmes, tries to keep his/her room tidy, goes shopping for small items, continues with some favourite hobbies, is orientated when in unusual surroundings [15]).

Both IADL scales include some items which are not applicable to all patients. Therefore, for comparative analysis, IADL scores had to be converted into a standard scale with ratings between 20 (maximum degree of ability) and 100 (minimum degree of ability) to allow for an indirect comparison of results.

Tolerability and safety were assessed at each examination and by spontaneous recording of adverse drug reactions according to the international standards of good clinical practice. Withdrawals from the studies were recorded together with the reason leading to early study termination.

Statistical Analysis

The analyses were based on the intent-to-treat population (ITT, patients with at least 1 assessment apart from baseline) and the per-protocol set (PPS, patients completing all visits of the NISs).

Descriptive statistics were used for baseline demographics and clinical characteristics as well as safety and tolerability. Repeated-measures analyses of variance (Hotelling's test) and paired t test were used to observe the difference in MMSE and IADL scores between visits. The multiple linear regression technique (stepwise/forward) and the appropriate univariate/non-parametric tests (t test, Pearson's correlation coefficient, ANOVA, Scheffé's test) were used to compare the relationship of both baseline values and the final changes in efficacy parameters (MMSE, IADL) with individual data (sex, age, severity of AD and pretreatment with ChEIs). Multiple logistic regression was applied in order to compare treatment discontinuation and adverse drug reactions with country and age.

Results

Patient Population

A total of 4,415 patients participated in both NISs. Out of those patients, 110 were excluded from the analysis due to an MMSE score at baseline of >27 (no dementia) or no documented treatment with memantine. The ITT population therefore included 4,305 patients, 2,570 in the Greek and 1,735 in the German study (table 1).

The mean age of the total patient population was 75.5 ± 7.5 years (56.7% were females). At baseline, the mean MMSE score was 17.1 ± 5.5, and 27.5% of the patients had already received ChEIs. Significant differences between the two countries were observed concerning age, sex, severity of AD, and pretreatment with ChEIs, where-

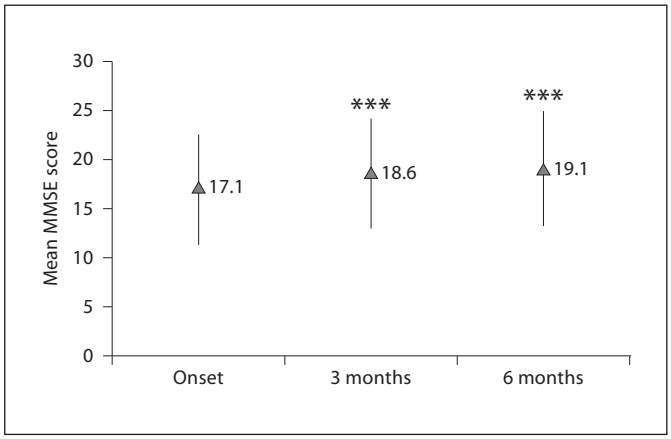

Fig. 1. Mean MMSE scores at baseline and after 3 and 6 months of treatment with memantine (ITT). The respective MMSE scores for the PP population (n = 3,257) are 17.1 ± 5.4, 18.6 ± 5.5, and 19.1 ± 5.7 score points. *** $p < 0.001$.

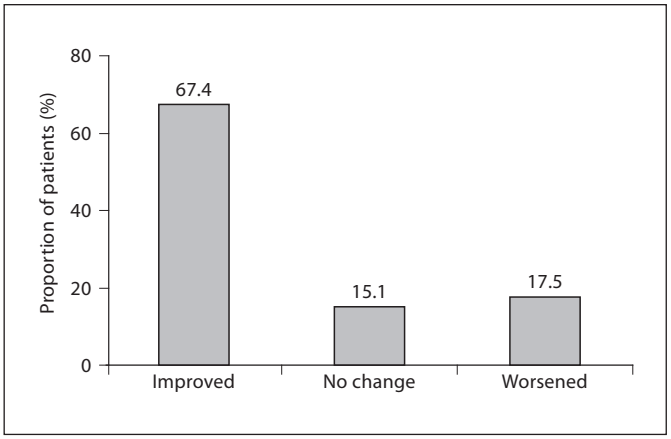

Fig. 2. Percentage of patients who revealed improvement, no changes or worsening after 6 months of treatment with memantine compared to baseline (ITT).

Table 1. Patient characteristics at baseline

	Country				Total	
	Greece		Germany			
	n	%	n	%	n	%
Female	1,402	54.6	1,013	60.1	2,415	56.7
Age groups						
≤65	192	7.5	184	10.8	376	8.8
66–75	1,163	45.3	547	32.1	1,710	40.0
>75	1,215	47.3	975	57.2	2,190	51.2
Severity of AD at baseline (MMSE score)						
Mild (≥20)	1,095	42.6	438	26.7	1,533	36.4
Moderate (10–19)	1,314	51.1	948	57.8	2,262	53.7
Severe (≤9)	161	6.3	254	15.5	415	9.9

by the German population included more females (60.1 vs. 54.6% in the Greek population), older patients (76.4 ± 8.3 vs. 74.8 ± 6.8 years, respectively), in a more severe stage of disease (15.7 ± 5.8 vs. 18.0 ± 5.1 MMSE score points, respectively), and fewer patients receiving ChEIs (16.9 vs. 34.2%, respectively, $p < 0.001$ for all comparisons).

Efficacy

Treatment with memantine led to a significant improvement of symptoms relating to cognition and activities of daily living in the total population. Efficacy outcomes were not found to be correlated with age or sex.

Cognition

After 6 months of treatment, MMSE had significantly improved by 2.0 ± 3.7 score points in the ITT population ($n = 3,924$, $p < 0.001$), and the mean improvement observed did not differ between the ITT and PPS population (fig. 1).

The comparison between the Greek (MMSE score improved by 1.8 ± 3.1 score points, ITT) and the German population (MMSE score improved by 2.3 ± 4.4 score points, ITT) did not reveal any significant differences. Accordingly, in a responder analysis, the mean MMSE scores increased in 67.4% of the patients of the ITT population (PPS 66.9%), and stabilization was shown in 15.1% (PPS 15.0%) of the patients after 6 months of treatment. In contrast, worsening was observed in 17.5% (PPS 18.0%) of the patients (fig. 2).

Instrumental Activities of Daily Living

In the total population, there was a significant improvement of IADL by 4 ± 11.5 points compared to baseline in the ITT population ($n = 3,545$, $p < 0.001$), and the mean improvement rate observed did not differ between the ITT and PP population (fig. 3).

When comparing the improvement of IADL in the Greek (IADL –4.4 ± 10.7, ITT) and the German population (IADL –3.4 ± 12.4, ITT), no significant difference could be shown to exist between the countries.

Tolerability and Safety

The safety population included 4,305 patients. 635 patients (14.8% of the safety population) discontinued treat-

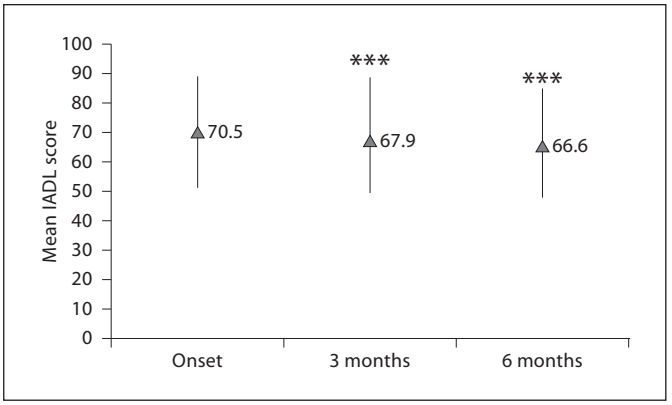

Fig. 3. Mean IADL scores at baseline and after 3 and 6 months of treatment with memantine (ITT). The respective IADL scores for the PP population (n = 2,990) are 70.9 ± 18.6, 68.2 ± 18.5, and 66.8 ± 18.9 score points. *** $p < 0.001$.

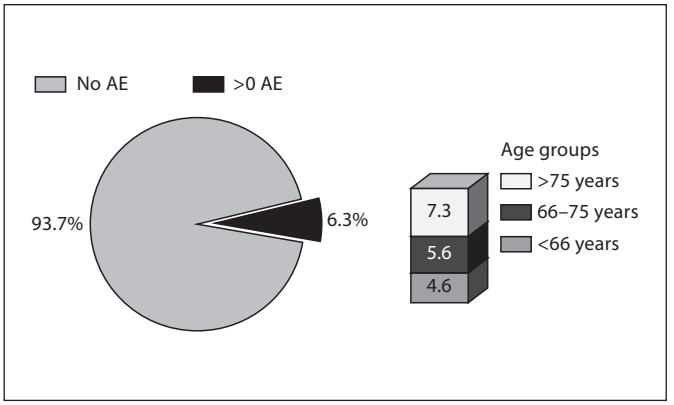

Fig. 4. Proportion of patients with at least 1 AE out of the safety population (left) and AEs stratified by age group (right).

Table 2. Patients with AEs

	Total (n = 3,910)	
	n	%
Psychiatric disorders	100	2.55
General disorders and administration site conditions	75	1.92
Nervous system disorders	65	1.66
Gastro-intestinal disorders	29	0.74
Cardiovascular disorders	23	0.59
Endocrine, metabolism and nutrition disorders	12	0.31
Ear, nose and labyrinth disorders	9	0.23
Respiratory, thoracic and mediastinal disorders	9	0.23
Musculoskeletal, connective tissue and bone disorders	5	0.13
Skin and subcutaneous tissue disorders	4	0.1
Infections	3	0.08
Renal and urinary disorders	3	0.08
Neoplasmatic disorders	3	0.08
Reproductive system and breast disorders	3	0.08
Blood and lymphatic disorders	2	0.05
Total number of AEs	345	8.8
Total number of patients with AEs	245	6.3

ment prematurely, 487 in the Greek and 148 in the German sample. The most frequent reason for treatment discontinuation was 'Patient did not attend the assessment visits', which occurred in the Greek population only (403 patients, 9.4%). Further reasons for treatment discontinuation were the patient's or caregiver's wish to terminate treatment (1.6%), treatment failure (1.5%) or other reasons not further specified (1.3%). Excluding patients on account of the previously mentioned reasons and without recorded adverse events (AEs), the safety population further analysed included 3,910 patients, of which 245 experienced at least one AE (345 AEs; fig. 4).

Concerning the occurrence of AEs, there was a significant correlation between age and the number of AEs, with older patients showing a higher rate of AEs ($p < 0.001$; fig. 4). The most frequent AEs belonged to psychiatric (2.55%), general (1.92%) or nervous system disorders (table 2).

Upon comparing the safety population of the Greek study with the safety population in the German study, significant differences were discovered in the number of patients who discontinued treatment and in the number of AEs. More specifically, the percentage of premature discontinuation of treatment was more than twice as high in Greece as it was in Germany (18.9 vs. 8.5%, $p < 0.001$). The same holds true for the recorded AEs (8.4 vs. 3.6%, respectively, $p < 0.001$). In addition, premature discontinuation of treatment was more frequent in the less severe cases and the recorded AEs were more frequent in older patients ($p < 0.001$).

Discussion

Along with RCTs, NISs prove the beneficial effects as well as the safety and tolerability of a treatment option. In contrast to RCTs with limited numbers of patients and strict inclusion/exclusion criteria, NISs reflect a broader

spectrum of patients including those with concomitant disease. 44.5% of the patients included in the German NISs had hypertension, 24.0% had heart failure, 19.7% arteriosclerosis and 17.2% diabetes mellitus [12]. These figures underline the value of NISs in everyday clinical routine.

In the current analyses, memantine significantly improved cognitive performance in patients with AD by 2 MMSE points in the course of the treatment period, without revealing any country-specific differences. This improvement is reflected especially by the greater percentage of patients classified as being in a mild stage of AD after 6 months of treatment compared to baseline. In responder analyses based on RCTs, it was shown that fewer patients treated with memantine underwent a decline in their cognitive abilities compared to placebo [11], and the results of both NISs and responder analyses support each other.

A similar significant improvement was seen in the current analyses regarding IADL, which was also supported by the responder analyses [11]. A possible shortcoming of the current analyses is the fact that the NISs used different scales to assess the activities of daily living and only a subset of items could be applied. However, the results published in the primary papers showed an improvement of symptoms based on the complete scales used in the respective NIS [12, 13].

Whereas efficacy results obtained in both countries are comparable, noticeable differences can be seen in the study populations regarding age, severity of the disease and pretreatment with ChEIs, with German patients being older, in a more advanced stage of AD and less receiving ChEIs. Even though the reasons for these differences are unknown, it can be assumed that the perception of AD and the therapeutic options might differ in both countries, both from a patient's and caregiver's point of view as well as from a physician's point of view [2, 16]. Recent results from an AD survey conducted in five countries [17] have shown that 42% of interview partners in Germany confirmed that they had an effective treatment for AD, whereas only 27% made this assertion in Spain. In addition, the perception of symptoms differs in the various countries: in Germany, 'remembering' is regarded as the key symptom of AD (76%), a feature which is less important in Spain (44%). However, there are no data that apply to Greece, and examples given are a hint rather than an explanation for differences between Greece and Germany. Furthermore, the question regarding the premature study terminations in the Greek NISs remains to be answered. They might be attributed to differences in the patients' compliance to the physician, with a possible closer relationship existing between the patient and 'their' practitioner in Germany. It would be of interest to examine which external factors and perceptions are the drivers for the differences observed when comparing different study populations.

Nevertheless, the analyses of both single and merged patient populations showed the efficacy, safety and tolerability of memantine in the treatment of AD in a broad population of real-life patients.

Disclosure Statement

A. Galanopoulos and W. Janetzky are employees of Lundbeck. The studies were sponsored by Lundbeck.

References

1 Galasko D, Bennett D, Sano M, Ernesto C, Thomas R, Grundman M, Ferris S, the Alzheimer's Disease Study Group: An inventory to assess activities of daily living for clinical trials in Alzheimer's disease. Alzheimers Dis Assoc Disord 1997;11:33–39.

2 Georges J, Jansen S, Jackson J, Meyrieux A, Sadowska A, Selmes M: Alzheimer's disease in real life – The dementia carer's survey. Int J Geriatr Psychiatry 2008;23:546–551.

3 Hallauer JF, Schons M, Smala A, Berger K: Untersuchung von Krankheitskosten bei Patienten mit Alzheimer-Erkrankung in Deutschland. Gesundh Ökon Qual Manage 2000;5:73–79.

4 Geldmacher DS, Froelich L, Doody RS, Erkinjuntti T, Vellas, B, Jones RW, Banerjee S, Lin P, Sano M: Realistic expectations for treatment success in Alzheimer's disease. J Nutr Health Aging 2006;10:417–429.

5 DGPPN, DGN (eds): Diagnose- und Behandlungsleitlinie Demenz. Heidelberg, Springer, 2009.

6 Hort J, O'Brien JT, Gainotti G, Pirttila T, Popescu BO, Rektorova I, Sorbi S, Scheltens P, on behalf of the EFNS Scientist Panel on Dementia: EFNS guidelines for the diagnosis and management of Alzheimer's disease. Eur J Neurol 2010;17:1236–1248.

7 IQWiG: Responderanalysen zu Memantin bei Alzheimer Demenz. 2011. Report No 84. https://www.iqwig.de/download/A10-06_Rapid-Report_Responderanalysen_zu_Memantin_bei_Alzheimer_Demenz.pdf

8 NICE: Dementia. Supporting people with dementia and their carers in health and social care. NICE Clinical Guideline 42, 2011. http://www.nice.org.uk/nicemedia/live/10998/30318/30318.pdf

9 Ruether E, Schnitker J, Janetzky W, Friede M: Efficacy of memantine in patients with Alzheimer's disease: meta-analyses of 9 clinical trials. Poster Alzheimer's Association International Conference, Paris, 2011.

10 Winblad B, Jones RW, Wirth Y, Stöffler A, Möbius HJ: Memantine in moderate to severe Alzheimer's disease: a meta-analysis of randomised clinical trials. Dement Geriatr Cogn Disord 2007;24:20–27.
11 Hellweg R, Wirth Y, Janetzky W, Hartmann, S: Efficacy of memantine in delaying clinical worsening in Alzheimer's disease: responder analyses of nine clinical trials with patients with moderate to severe AD. Int J Geriatr Psychiatry 2011, E-pub ahead of print.
12 Calabrese P, Essner U, Förstl H: Memantin in der klinischen Anwendung: Erfahrungen aus der Praxis. Psychopharmakotherapie 2006;13:64–69.
13 Stamouli SS, Tzanakaki M, Giatas S, Georgiadis G, Papalexi E, Parashos IA: An open-label, multicenter observational study of patients with Alzheimer's disease treated with memantine in the clinical practice. Dement Geriatr Cogn Disord 2011;1:10–19.
14 Lawton MP, Brody EM: Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontologist 1969; 9:179–186.
15 Spiegel R, Brunner C, Ermini-Führschilling D, Monsch A, Notter M, Puxty J, Tremmel L: A new behavioural assessment scale for geriatric out- and in-patients: the NOSGER (Nurses Observation Scale for Geriatric Patients). J Am Geriatr Soc 1991;39:339–347.
16 Riepe MW, Ibach B: Neurological and psychiatric practitioner's views on Alzheimer's disease and treatment thereof. Dement Geriatr Cogn Disord 2008;26:541–546.
17 Blendon RR, Benson JM, Weldon KF: Five-country Alzheimer's disease survey. 2006. http://www.alzheimer-europe.org/EN/Research/Value-of-knowing/Public-concerns-about-Alzheimer-s-disease.