

Memantine (Ebixa®) in Clinical Practice – Results of an Observational Study

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Key Words

Memantine · Alzheimer's disease · Cognition · Observational study · N-methyl-D-aspartate receptor antagonist

Abstract

Background/Aims: In a post-marketing observational study, the efficacy and tolerability of memantine were examined in patients with moderate to severe Alzheimer's disease. **Methods:** The patients were treated with 20 mg/day of memantine for a 6-month period. The efficacy of memantine was evaluated using the Mini-Mental State Examination, the Nurses' Observation Scale for Geriatric Patients (NOSGER) and the Explorationsmodul Demenz (EMD) scale. In addition, a global assessment was made by the physician. **Results:** After 6 months of open-label treatment with memantine, the patients' cognitive function, ability to perform daily activities and global performance all showed a marked improvement. In the overall evaluation by the physician, improvement or stabilisation had been achieved by 78.8% of patients after 6 months of therapy. Memantine also demonstrated an excellent tolerability profile. **Conclusion:** The results of this naturalistic study support the significant efficacy and tolerability of memantine that has been previously demonstrated in randomised, controlled clinical Alzheimer's disease trials.

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Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative condition. In Germany, there are an estimated 900,000 patients with dementia, of whom 650,000 suffer from AD [1]. Every year, 200,000 new cases of dementia are diagnosed, including approximately 120,000 cases of AD [1]. Age is still considered to be the greatest risk factor for dementia, so, with the proportion of elderly people increasing in the population, it is anticipated that the number of cases of dementia will continue to rise [1].

Alongside the cholinergic deficit seen in AD [2], disturbances in the glutamate system also occur [3]. Glutamate is the most important excitatory neurotransmitter because approximately 70% of all excitatory CNS synapses are glutamatergic [3]. Although not all of the processes involved in the pathogenetic mechanism are known, there are numerous specific findings regarding the emergence of impaired neurotransmission and neuronal cell death, as well as the role of glutamate. In AD, there is a rise in the concentration of glutamate in the synaptic cleft, either through increased release into the cleft or through reduced reabsorption out of the cleft [4]. This increase in glutamate not only leads to disruption of signal transduction but also causes excitotoxic effects [4, 5].

There are currently 2 approved therapeutic options for the treatment of AD: cholinesterase inhibitors (ChEIs), which counteract the cholinergic deficit [6, 7], and me-

mantine, an uncompetitive N-methyl-D-aspartate receptor antagonist that improves neuronal signal transduction and demonstrates neuroprotective properties [4, 8]. While ChEIs are approved for the treatment of mild to moderate AD, memantine has been a therapy option for the advanced stages of AD since 2002. In controlled clinical studies among patients with moderate to severe AD, memantine has demonstrated efficacy and tolerability both as a monotherapy and in combination therapy with a ChEI [9–11]. The efficacy of memantine was also shown for milder forms of AD [12]. In these placebo-controlled, double-blind studies, memantine was significantly superior to placebo in the areas of cognition, ability to perform activities of daily living and overall clinical impression.

Due to strict inclusion and exclusion criteria, only very select patient populations are examined in clinical studies, and therefore the aim of the observational study described here was to examine the efficacy and tolerability of memantine under naturalistic conditions, i.e. in a heterogeneous patient population in daily practice. In order to meet with the quality assurance requirements imposed on observational studies, a multidimensional questionnaire with options for self-evaluation and external evaluation by the caregiver was used.

Methods

In an open-label, multi-centre post-marketing observational study, patients with AD were treated with 20 mg/day of memantine for 6 months. The physicians who participated were primarily in private practice (general medicine practitioners, neurologists and psychiatrists).

Patient Population

A total of 2,000 patients with moderate to severe AD (based on ICD-10 criteria) were accepted into the observational study. No specific requirements were in place for the selection of patients, apart from an attending physician's positive diagnosis of dementia made in accordance with clinical criteria. The exception was that the patients were not allowed to participate in a clinical trial at the same time because therapy with memantine could have been incompatible with the trial medication. Also, the contraindications and safety measures listed in the memantine prescribing information had to be observed.

Outcome Measures

At the beginning of the study, demographic data and information on any previous therapy with antidementia drugs, and any concomitant diseases and medications, was collected. The patients were examined at 3 points during the study – during an initial examination and subsequently at efficacy evaluations after 3 and 6 months. At each examination, the Mini-Mental State Ex-

amination (MMSE) [13] and the Nurses' Observation Scale for Geriatric Patients (NOSGER) [14] were used to test cognitive performance and to externally evaluate the patients' ability to perform activities of daily living, respectively. Alongside these assessments, the Explorationsmodul Demenz (EMD) (Dementia Exploration Module) was used in the initial and 6-month examinations (manuscript in preparation). The EMD is a psychometric questionnaire that uses 13 simple closed questions on the areas of cognition (area A), everyday behaviour and affectivity (area B), and disease-related self-awareness (area C). The responses are used to generate a self-evaluation, as well as a collateral evaluation of the patient's condition, with respect to the negative effects of dementia on activities of daily living and to the subjective perception of such effects. This process makes an evaluation of memory and other cognitive disruptions possible, as well as an assessment of independence, communication, mood and motivation. This dimension-specific evaluation is performed by the patient and by the caregiver.

The overall clinical impression was evaluated by the treating physician according to a 3-step scale (improved, stabilised, deteriorated). The effect of memantine on cognitive abilities and the ability to perform activities of daily living was assessed using a 4-step scale (very good, good, fair and poor). Tolerability was evaluated by the physician in the same way. At each examination point, the patients were asked whether they had experienced any adverse events (AEs), and these were documented according to international standards of good clinical practice. The dosage of memantine was recorded after 3 and 6 months. In the case of premature termination of the therapy, the reasons for cessation were ascertained.

Statistical Analysis

Statistical analysis of the effects of treatment was performed using parametric tests. Individual missing values were not taken into account when analysing the data collected after the 3- and 6-month time points – 'observed case' population. With respect to safety and tolerability, the analysis was descriptive.

Results

Patient Characteristics

A total of 1,845 patients were included in this observational study. It was possible to evaluate efficacy data from 1,580 patients, with 265 being excluded for various reasons (>1 answer was possible): for 72 patients, no treatment documentation was available, for 60 there was no evaluation after 3 or 6 months, a further 73 had MMSE scores of >27, and for 130 patients, retrospective documentation was the reason for exclusion.

Newly diagnosed cases were included in the study alongside patients with existing AD diagnoses (table 1). The mean age of the patients included in the study was 76.3 ± 8.7 years, and 58.2% were female (table 1). A total of 60.9% of the patients had received prior treatment for AD, and of these (taking into consideration multiple an-

Table 1. Patient characteristics

Sex, % female	58.2
Mean age \pm SD, years	76.3 \pm 8.7
Mean height \pm SD, cm	167.1 \pm 8.1
Mean weight \pm SD, kg	70.3 \pm 11.5
Mean duration of AD \pm SD, years	2.4 \pm 1.9
Concomitant diseases (% patients)	
Hypertension	44.5
Heart failure	24.0
Arteriosclerosis	19.7
Other cardiac diseases	2.6
Diabetes mellitus	17.2
Other	22.4
Mean MMSE score at baseline \pm SD (n = 1,496)	15.4 \pm 5.7

Concomitant diseases: multiple answers possible.

swers), 24.9% had received ginkgo extracts, 20.1% piracetam, and 17.3% had taken ChEIs. Additionally, during the study, 21.6% of the patients also received another antimentia drug. Along with AD, 74.4% suffered from at least 1 additional concomitant disease, the most common of these being cardiovascular disease (table 1). Correspondingly, comedication was indicated for 65.4% of the patients, with 41.2% receiving antihypertensive drugs. In addition, cases of comedication included the use of anti-diabetic drugs (13.4%), antidepressants (11.3%) and neuroleptic drugs (9.3%).

At the initial examination, the mean MMSE score was 15.4 ± 5.7 . The mean doses of memantine received were 17.1 ± 5.8 and 17.3 ± 5.8 mg after 3 and 6 months, respectively. In total, 185 patients (10.1%) terminated memantine therapy before completion of the 6-month observation. The reasons indicated were patient's wishes (3.4%), lack of efficacy (3.3%), AEs (3.1%) or other reasons (2.4%) (multiple answers possible).

Efficacy

Memantine led to an improvement in symptoms as determined by all the examination measures in this study (cognition, activities of daily life and physician's global assessment). After 6 months of therapy, the MMSE had improved by 2.5 ± 4.5 points (n = 1,199; $p < 0.0001$; fig. 1), and in the responder analysis, the MMSE score increased by at least 1 point in 68.2% of the patients (fig. 2). An improvement of 1–2 points was seen in 17.0% of the patients, a further 34.4% improved by 3–6 points, and the scores for 16.8% of the patients increased by >6

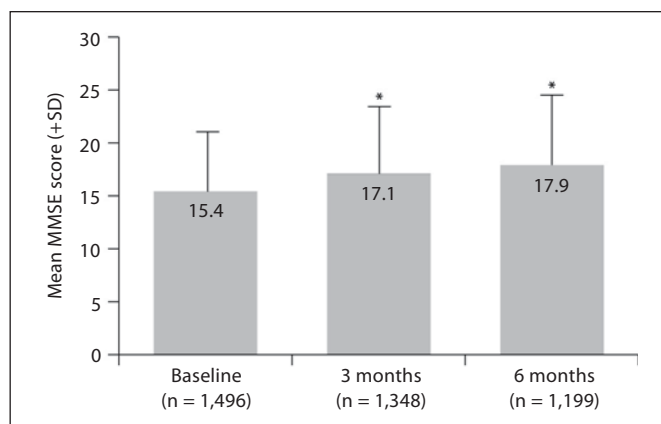


Fig. 1. Mean MMSE scores at baseline and after 3 and 6 months of treatment with memantine (observed case analysis). * $p < 0.0001$ vs. baseline; t test.

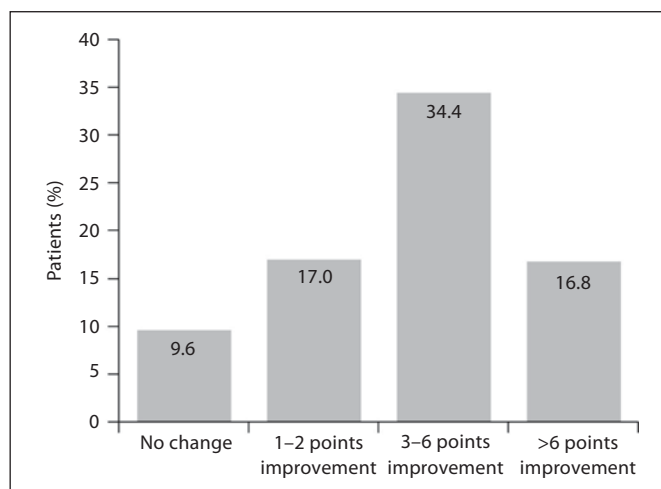


Fig. 2. Responder analysis – patients (percent) with stabilisation or improvement (1 to ≥ 6 points) in MMSE score after 6 months of treatment with memantine (vs. baseline).

points. Stabilisation of core cognitive symptoms was shown in 9.6% of the patients (fig. 2).

With the NOSGER, a significant improvement over the initial values in all 6 dimensions was observed after 3 and 6 months (fig. 3).

Changes to the individual dimensions of the EMD over the study period were calculated as the change from baseline in the median number of overall points in each dimension (fig. 4). This showed a significant ($p < 0.0001$) decrease (improvement) in the patient and external (care-

Fig. 3. Improvement in NOSGER items after 3 and 6 months of treatment with memantine (vs. baseline). $p < 0.0001$ vs. baseline at 3 and 6 months, for all items. $p \leq 0.0001$ 3 months vs. 6 months. IADL = Instrumental activities of daily living; ADL = activities of daily living.

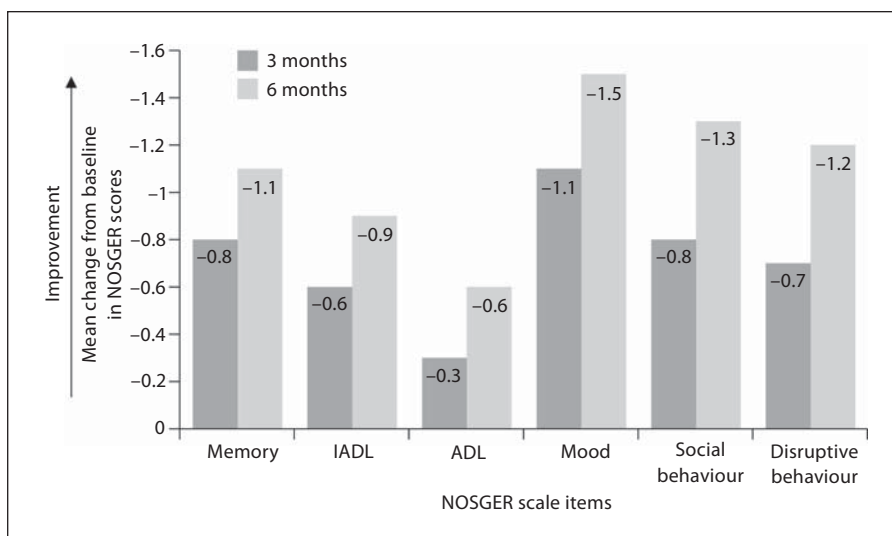
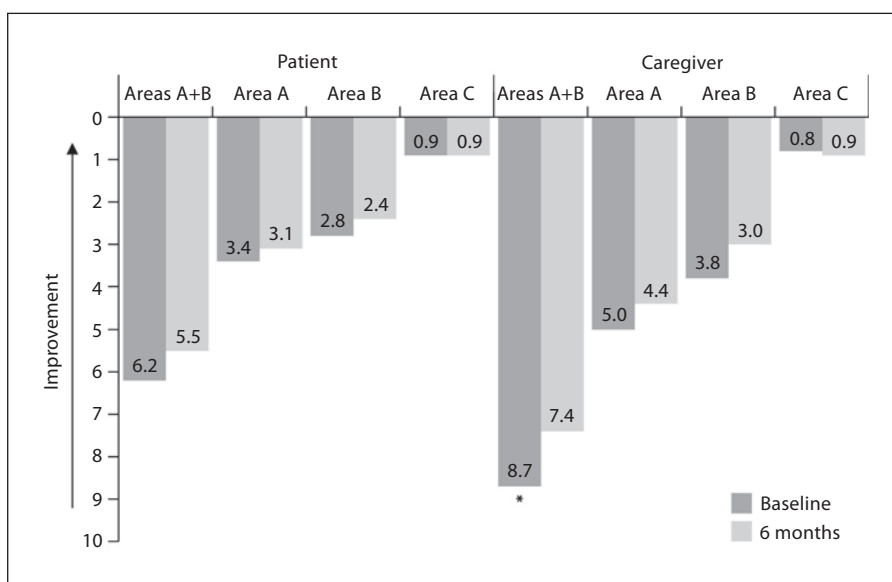


Fig. 4. Mean EMD scores for each area at baseline and after 6 months of treatment with memantine. * $p < 0.0001$. A = Cognition; B = everyday behaviour and affectivity; C = disease-related self-awareness.



giver) assessments of daily performance with respect to the EMD total score. The clearest improvement was seen in the 'social behaviour' dimension for both the self-assessment and the external (caregiver) assessment.

Moreover, for the MMSE as well as the NOSGER, effect sizes for individual items of each scale were calculated. In this process, the difference between the baseline data and the result of the interim measurement after 3 months (interval effect, for NOSGER and MMSE) or at the end of the observation period after 6 months (primary effect, for NOSGER and MMSE) was compared. For the NOSGER, the largest effect sizes were shown in the 'mood' and 'disturbing behaviour' dimensions, and

in the MMSE it was the items 'orientation' and 'recall', in particular, that contributed to the primary effect.

In the overall evaluation by the treating physician, stabilisation of, or improvement in, symptoms had been achieved in 78.8% of the patients after 6 months of therapy (fig. 5). In evaluating cognitive performance after 6 months of treatment with memantine, a very good or good effect was indicated for 37.6% of the patients, a moderate effect for 40.9%, and for 16.2% of the patients, cognitive performance was evaluated as being poor (fig. 6). A similar pattern was seen in the evaluation of efficacy with respect to activities of daily living. For 47.7% of the patients, this was indicated as being very good to good,

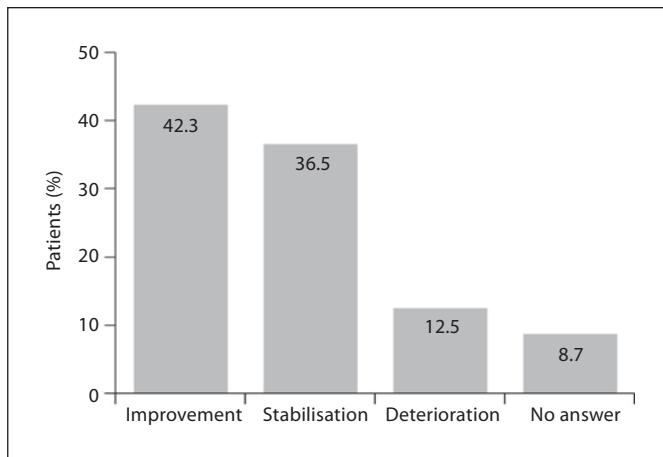


Fig. 5. Physician's overall clinical evaluation after 6 months of treatment with memantine.

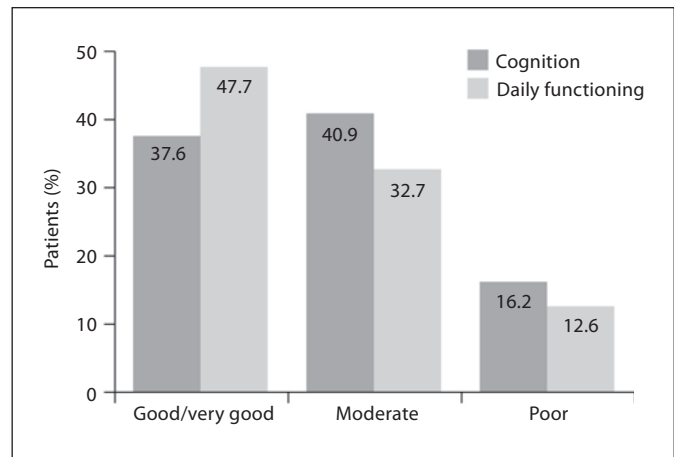


Fig. 6. Physician's global evaluation of cognition and daily functioning after 6 months of treatment with memantine.

in 32.7% it was moderate, and for 12.6% of the patients, efficacy was deemed to be poor (fig. 6).

Safety and Tolerability

A total of 87 (4.7%) out of 1,845 patients experienced at least 1 AE during the study, with 224 AEs documented in all. Of these AEs, 58% appeared to have no connection with the memantine treatment, and no particular trends in AEs were observed, with a wide variety of different events reported. The most frequently reported AEs were either psychiatric (1.8%) or neurological (1.7%), with all other organ systems being affected in <1% of the patients. The most common AEs ($\geq 0.2\%$) are listed in table 2. Of these, 2.7% were classified as severe AEs, the majority of which led to hospitalisation because of either a deterioration in the patient's overall state or an existing concomitant disease. For 87.8% of the patients with severe AEs, no connection with the therapy was seen.

In total, 24 out of 1,845 patients (1.3%) died during the observation study. The most frequent causes were cardiovascular diseases, apoplexy, pneumonia and deterioration in the overall state of the patient or senile atrophy. In 23 of these patients, anamnestic cardiovascular diseases, diabetes mellitus, arteriosclerosis and/or conditions following apoplexy were documented, however, memantine was not believed to be the cause in any of these cases.

The good level of tolerability of memantine was also reflected in the physicians' global evaluation, where tolerability was classed as very good in 63% of the patients and good in a further 30%.

Table 2. Patients with adverse events (incidence $\geq 0.2\%$)

Adverse event	Patients, %
Restlessness	0.5
Dizziness	0.4
Pneumonia	0.4
Deterioration of AD	0.4
Confusion	0.3
Cerebrovascular events	0.3
Heart failure	0.3
Aggression	0.3
Dehydration	0.3
Nausea	0.2
Paranoia	0.2
Agitation	0.2
Urinary tract infection	0.2

Discussion

In the post-marketing observational study described here, the efficacy and tolerability of memantine were demonstrated in a heterogeneous patient population.

Whilst the clinical testing of medications is typically carried out on a relatively small number of patients who have been selectively chosen for clinical examination, the results of observational studies tend to provide a more accurate reflection of daily practice. In these observational studies, inclusion and exclusion criteria are usually broadly structured and because of this, these studies

tend to have more naturalistic conditions when compared to clinical examinations. For this reason, any rare or very rare adverse effects, interactions or other dangers in connection with the use of the medication can be recognised more frequently in observational studies. Knowledge of the efficacy, safety and interactions of a medicine tends to be incomplete when it is first approved. New findings regarding the safety of medications can arise long after the approval of the drug, and sometimes the particular interactions of well-known substances are only discovered at a later date, following new developments in medical science. Consequently, it appeared to be sensible to conduct a broadly structured study of the efficacy and tolerability of memantine with a representative patient sample. Furthermore, the Arzneimittelgesetz (Pharmaceuticals Act) of the Federal Republic of Germany requires that additional, systematic gathering and analysis of information on pharmaceuticals should be carried out even after they have been approved for medicinal use.

Over the course of 6 months of treatment with memantine, it was possible to document any stabilisation or improvement of the patients' AD using the MMSE. At the end of the 6-month observation, the MMSE score had improved significantly, with a responder analysis revealing that 68% of the patients had improved MMSE scores. In a meta-analysis based on cognitive decline in AD patients, Han et al. [15] showed that MMSE scores declined in untreated patients by 3.3 points annually. By contrast, the average MMSE value in the examination discussed here rose by 2.5 points, indicating a clear improvement in cognitive symptoms. The results of the NOSGER also indicated an improvement in memory, activities of daily living and behaviour. This effect was most evident in the areas of mood as well as in behavioural dimensions. In addition, after 6 months of treatment with memantine, this positive effect was even more pronounced for individual items of these scales. With this therapeutic approach, it was thus possible to obtain an effect comparable to that documented under cholinergic therapy with donepezil [16].

The average EMD scores showed a statistically significant decrease after the 6-month observation in both self-evaluation and caregiver-referenced evaluation. Interestingly, the daily functions initially rated by the caregiver as being the most adversely affected were those that underwent the most improvement in the caregiver evaluation at the end of the observation period. This may be viewed as a relevant reduction in caregiver burden.

The clinical relevance of these findings is borne out by the global evaluations. The evaluation of the overall clinical impression, as well as that of the efficacy of memantine with respect to cognition and daily functions, showed that the effects measured using the MMSE, NOSGER and EMD were also visible to the treating physician.

In controlled clinical studies over 6 months, it was possible to show that under therapy with memantine, stabilisation or improvement of symptoms occurred [9, 11, 12]. The observational study discussed here confirms that the effects demonstrated in clinical studies are relevant to everyday practice. However, for patients with advanced dementia, objective tools may not be the best way to measure these effects on cognitive performance due to floor effects. On the other hand, self-assessment of possible deficits can, for the same reasons, also lead to distortions. In fact, the EMD results under discussion show that subjective assessments by the patient and caregiver can differ substantially. Therefore, in the case of patients with advanced dementia, including those with reduced powers of judgement, it appears all the more important to include behaviour-related judgement items and, in particular, those relevant to activities of daily living and care, along with cognitive items.

With respect to the comorbidity of the patients and the necessary comedication, the tolerability of an antidementia therapy is especially important. In total, 74.4% of the patients included in this observational study suffered from at least 1 concomitant disease, with 60.7% citing cardiovascular diseases. Correspondingly, comedication was given to 65.4% of the patients. For 4.7%, at least 1 AE occurred, which, due to the general state of the patients' health, is to be viewed as a low rate. None of the individual AEs occurred at a frequency >0.5%. Furthermore, the AEs that did occur corresponded to those reported in clinical studies, but with a lower incidence [9, 10, 17]. Of the 1.3% of patients who died during the course of this 6-month observation study, which corresponds to the frequency observed in other clinical studies [9], anamnestic cardiovascular diseases, diabetes mellitus, arteriosclerosis and/or apoplexy were present. This percentage is also in line with the number of deaths expected due to the age structure of the population studied and the accompanying high number of patients who additionally presented with at least 1 further disease [18].

The results of this observational study have shown that the effects of memantine, which have already been demonstrated in clinical studies, can also be achieved in everyday practice. The results of this study are comparable with those of the observational study published by

Hager et al. [16], in which the efficacy of donepezil for AD was examined over a 3-month period. After 3 months of therapy, memantine demonstrates equally good efficacy. Memantine is, however, distinguished by its more favourable tolerability profile, which is maintained even beyond the conventional study period for observation studies and without any loss of efficacy.

Taken together, the results of the observation study presented here show that, because of its good efficacy and tolerability, memantine represents an appropriate therapy option for the treatment of the cognitive as well as the non-cognitive effects of moderate to severe AD. The positive results achieved by this intervention are shown using realistic investigative tools and can be observed in everyday treatment relevant to usual practice.

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