Post-authorisation efficacy and safety study of memantine (Memaxa®) in patients with moderate to severe Alzheimer's disease

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Abstract
Alzheimer's disease is the most common type of dementia. Its course can be influenced with cognitive modulators such as memantine, which is used for alleviation of symptoms in moderate to severe Alzheimer's disease. We report the findings of a non-interventional study of the safety and efficacy of memantine (Memaxa®) which included 177 female and male patients aged 79 ± 9 years. The efficacy of the medicine was assessed both by the physicians and the patients or their carers. Their satisfaction with the therapy was increasing from the first month to the end of the study. At the end of the study, 84.1% of the physicians were satisfied or very satisfied with the treatment. Increasing satisfaction with Memaxa® therapy was observed in several domains, including the effect of therapy on behavioural and psychological symptoms, cognitive performance and ability to perform activities of daily living. A similar increase in satisfaction was expressed in the patients' or carers' assessments of the therapy, which showed that 74.9% of them were satisfied or very satisfied. In as many as 95% of the patients, 20 mg of memantine was the final daily dose. Patients on memantine were using concomitant medications for central nervous system disorders, mostly antidepressants and antipsychotics. Memantine was well tolerated and no adverse events were reported by 81% of the patients. The results of the study have demonstrated that Memaxa® is an effective and safe medicine for the treatment of moderate to severe Alzheimer's disease.

Introduction

Alzheimer's disease (AD) is the most common cause of dementia. It is found in about 60% of all dementia patients and mainly affects older people. Its prevalence among people above the age of 65 years is 5–10% and increases with age, affecting 20–45% of dementia patients aged between 80 and 90 years. A new person with AD is diagnosed every 3 seconds. [1, 2] The course of the disease can be positively influenced with cognitive modulators, of which the following four are used in AD therapy: donepezil, rivastigmine, galantamine and memantine. Memantine is an N-methyl-D-aspartate (NMDA) antagonist. It acts on NMDA receptors and improves the transmission of nerve signals and memory. In the European guidelines memantine is described as a medicine for treating moderate to severe AD. [3, 4]

The study was carried out with the purpose to assess the efficacy and safety of memantine treatment in patients with moderate to severe AD.

Methods

This non-interventional efficacy and safety study of memantine (Memaxa®) in Slovenian patients with moderate to severe AD was conducted from June to December 2013. It included male and female patients with moderate to severe AD aged over 18 years. The number of patient visits was determined based on the clinical judgement of the physician. The patients had their first visit at inclusion in the study, the second visit after one month, the third visit after two months and the fourth visit after three months. During a three-week dose-titration period in the first month, the dose of Memaxa® was incrementally increased by 5 mg weekly up to the maintenance dose in most patients. [5]

Results

One hundred and seventy-seven female and male patients were included in the statistical analysis. The age of the patients was 79 ± 9 years. The study population consisted of 61 (34%) male and 115 (65%) female patients. One hundred and fifteen patients (65%) had not been treated for AD previously and 62 (35%) patients had been taking medication for AD previously. Donepezil was used by 11.9% of the patients, rivastigmine (transdermal patches) by 10.2%, galantamine by 6.8%, rivastigmine (capsules) by 3.4% and memantine by 3.4% of the patients.
At inclusion in the study (first visit), 160 (90%) patients did not need any additional therapy for AD and 16 (9%) patients were using additional medication. Eight (50%) patients among those needing additional therapy were taking rivastigmine (transdermal patches), 5 (31.2%) galantamine and 3 (18.8%) donepezil. After 3 months of memantine therapy, the number of patients still using concomitant medication for AD was reduced to13 (8.1%) (Figure 1). Seven (53.8%) of these patients were taking rivastigmine (transdermal patches), 3 (23.1%) donepezil, and 3 (23.1%) galantamine. Each of them had only one additional AD medicine.

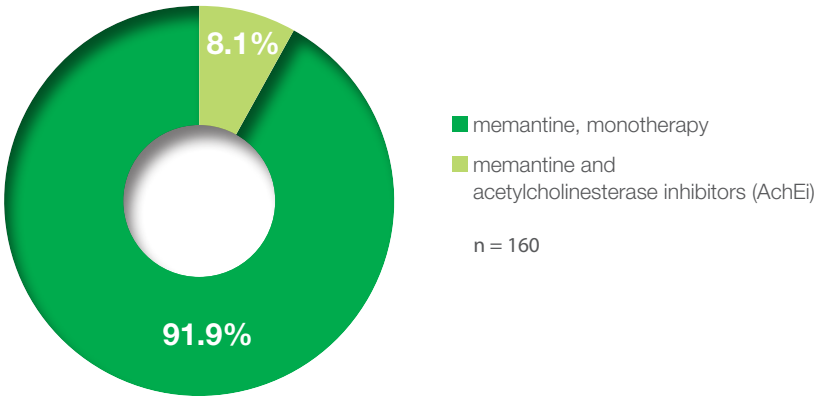
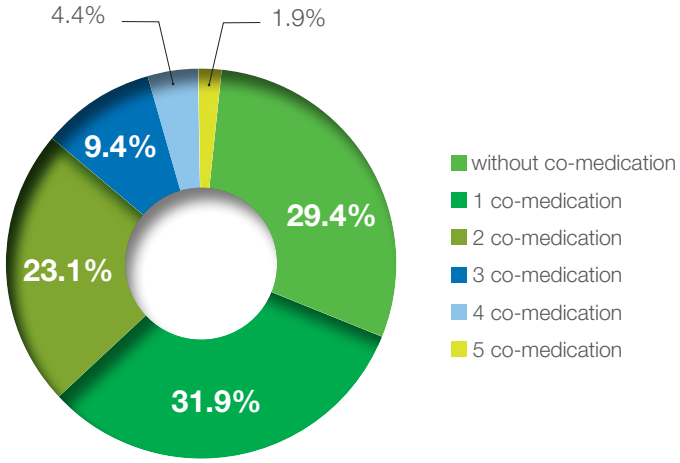


Figure1. After three months of therapy with memantine, as many as 92% of patients with moderate to severe AD did not need any additional antidementive medication.

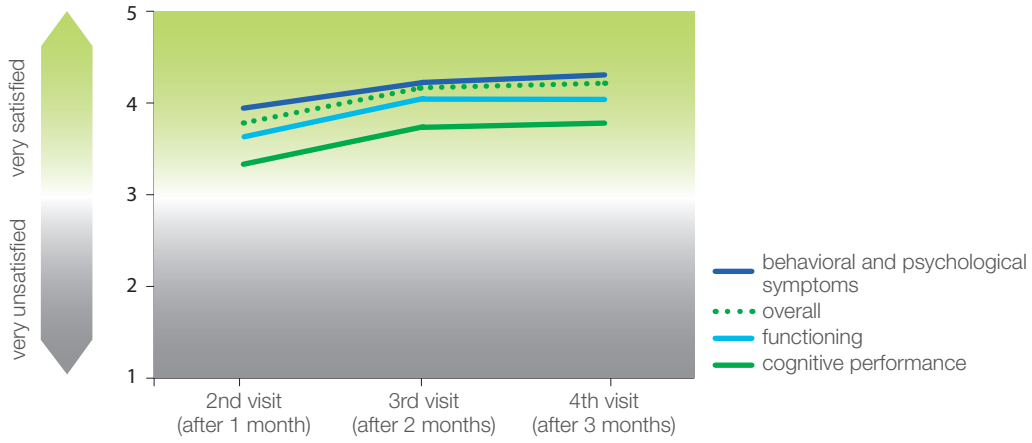
At the first visit, 120 out of 177 patients (67.8%) were on at least one medicine for other central nervous system disorders. Most of them were taking antidepressants (35.5%) and antipsychotics (32%). Concomitant hypnotics and sedatives were used by 14.3% of the patients, anxiolytics by 9.5%, anti-epileptics by 5.2% and anti-Parkinson medicines by 3.5%. After three weeks of therapy (fourth visit), 113 patients out of 160 (70.6%) were taking at least one medicine for the treatment of other central nervous system disorders (Figure 2). Most of them were taking antidepressants (34.7%) and antipsychotics (33.8%); 14.1% of them were taking hypnotics and sedatives, 8% anxiolytics, 5.6% anti-epileptics and 3.8% anti-Parkinson medicines. After three months of therapy, co-medication was very similar to that recorded at baseline. The most frequently co-prescribed antidepressants were sertraline and escitalopram, and the most frequently co-prescribed antipsychotic was quetiapine.



Figures may not total 100% because of rounding.

Figure 2. After three months of memantine therapy, 29.4 % of the patients were not receiving any additional medication for other central nervous system disorders and 70.6% of the patients were taking at least one such medicine.

The efficacy of memantine was assessed both by physicians and patients or carers. Apart from an overall assessment of satisfaction with the therapy the physicians assessed satisfaction with the effect of memantine on behavioural and psychological symptoms, cognitive performance and the ability to perform activities of daily living. They assessed satisfaction with the efficacy of Memaxa® on a 1- (very unsatisfied) to 5-point (very satisfied) grading scale. There was a continuous improvement in the physicians' overall assessment of satisfaction with the therapy from the first month onwards (Figure 3). The mean satisfaction score was 3.79 (score 3: 38.1% of the physicians, score 4: 36.8% and score 5: 22.6% of the physicians) after the first month (second visit), 4.17 at the third visit (score 3: 16.7% of the physicians, score 4: 50%, score 5: 33.3% of the physicians) and 4.23 at the last visit (score 3: 16.9% of the physicians, score 4: 43.1%, score 5: 40% of the physicians). At the end of the study, 84.1% of the physicians were satisfied or very satisfied with the therapy. They found that Memaxa® had the greatest effect on behavioural and psychological symptoms. The mean score in this domain was 4.31 at the last visit (score 3: 16.3%, score 4: 31.3%, score 5: 50.6%). The mean score in the domain satisfaction with the effect on the patient's ability to perform activities of daily living was 4.04 at the last visit (score 3: 21.3%, score 4: 40.6%, score 5: 34.4%). The mean score in the domain satisfaction with the effect on cognitive performance was 3.79 at the last visit (score 3: 32.5%, score 4: 38.1%, score 5: 23.1%).



The 95% confidence interval was within a range not differing from the mean by more than +/-0.15; $p < 0.0001$ in nay of the efficacy assessments

Figure 3. The efficacy of the therapy was continuously increasing from the first month of the treatment, as assessed by the physicians. The overall physicians' satisfaction score was 4.23 after three months of memantine therapy; the physicians found that memantine had the best effect on behavioural and psychological symptoms.

The patients or carers also assessed the efficacy of Memaxa® on a 1- to 5-point grading scale (1: very unsatisfied, 5: very satisfied). There was a continuous improvement in the overall score of the satisfaction with therapy, starting at the second visit. The mean satisfaction assessment score was 3.75 (score 3: 39.6%, score 4: 29.9%, score 5: 25.3% of the patients or carers) at the second visit and 4.09 at the third and fourth visits. At the last visit, a satisfaction score of 3 was reported by 22.6%, a satisfaction score of 4 by 38.4% and a satisfaction score of 5 by 36.5% of the patients or carers. The percentage of patients or carers satisfied or very satisfied with the treatment at the end of the study was 74.9%. The dose of memantine was adjusted during the first month of the study period. One hundred and seventy-two (97.2%) patients started treatment with a 5 mg dose, 1 patient with a 10 mg dose and 5 patients with a 15 mg dose. As many as 95% of the patients were on the maximum dose of memantine of 20 mg after 3 months of treatment and the mean daily dose was 19.5 mg. Tolerability was good. One hundred and forty-one (81%) patients did not experience any adverse reactions (Figure 4). Thirty-three patients (19% of the total population) experienced at least one adverse event related to memantine. No adverse reactions causally related to the treatment were reported in 81% of the patients. The most common causally related adverse reaction was headache, which occurred in 13 (7.5%) patients. Somnolence occurred in 11 (6.3%) patients and dizziness in 9 (5.2%) patients.

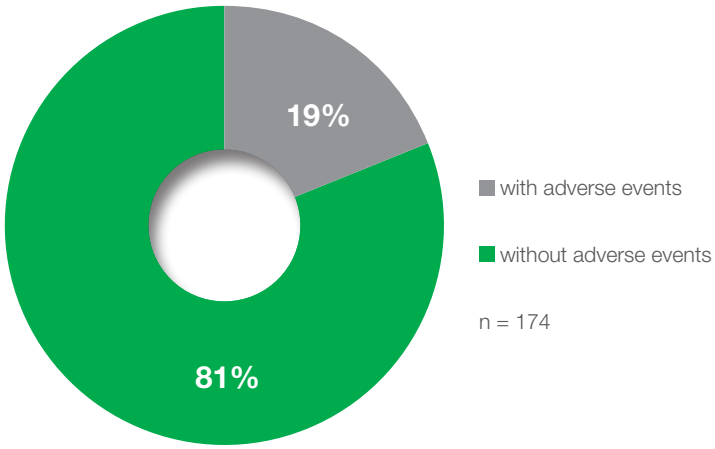


Figure 4. Memantine was well tolerated; 81% of the patients did not experience any adverse events

The treatment was discontinued due to adverse events in only 1 (0.6%) patient. No intervention for adverse events was required in 25 (14.4%) patients; symptomatic treatment was needed in 5 (2.9%) patients and dose reduction in 2 (1.2%) patients.

Discussion

Dementia impairs cognitive performance and the ability to perform the activities of daily living. People with dementia develop behavioural and psychological symptoms. The disease imposes a considerable burden on the patient and on his or her carer. Alzheimer's disease is treated symptomatically and the described phenotype is the primary target of treatment.[6] This non-interventional study was carried out to demonstrate the efficacy and safety of memantine in patients with moderate to severe AD. As early as in the first month after the introduction of memantine, satisfaction with the treatment was reported to be linked to several aspects of the disease and included an improvement of cognitive performance, functioning and behavioural and psychological symptoms in the physicians' assessment. At the end of the study, after four months of therapy, 84.1% of the physicians were satisfied or very satisfied with the treatment. They found that memantine had the most marked effect on behavioural and psychological symptoms. Among the patients and carers 74.9% of them were satisfied or very satisfied with the therapy. Memantine was well tolerated.

Slovenian patients with AD (n = 75) participated in 2013 in an epidemiological study.[7] The results of that epidemiological study agree in the following three aspects with the results of the present non-interventional efficacy and safety study: treatment habits, memantine doses used and co-medication in AD patients. The percentage of previously untreated patients with moderate AD in this non-interventional study was 63.5% and was similar to that reported in the epidemiological study (65%), which suggests late detection of AD. The daily dose of memantine at the end of the observation period was 20 mg in most patients in both studies (95% in the non-interventional study and 88% in the epidemiological study). The results of other studies have also shown that the 20 mg daily dose is the target daily dose of memantine. [8-12] The epidemiological study has demonstrated that if physicians prescribe the 20 mg dose they decide for the single-tablet regimen (in 95.5% of the patients).[7]
The single-tablet regimen reduces the carer's burden and improves the patient's compliance with the treatment regimen. An independent study investigating different regimens of medical treatment of dementia showed superiority of simpler regimens over the complex ones.[13] The results of both studies on memantine in AD have demonstrated that AD patients (68–85%) are using several medicines for the treatment of central nervous system disorders.[5, 7] Considering that memantine has been associated with a low risk of interactions with other medicines, it is reasonable to use it in these patients.[14]

Conclusion

We can conclude on the basis of the results of this non-interventional study that Memaxa® is an effective and safe medicine for the treatment of moderate to severe Alzheimer's disease, contributing to treatment satisfaction.

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14 Summary of Product Characteristics, Memaxa®.

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