ORIGINAL ARTICLE

Effect of donepezil in patients with Alzheimer’s disease previously untreated or treated with memantine or nootropic agents in Germany: an observational study

Tatjana Klinger*, Bernd Ibach*, Peter Schoenknecht*, Martin Kamleiter*, Gabriele Silvera, Johannes Schroeder and Ruediger Mielke†

*Staedt. Klinikum St. Georg, Verbund Gemeindenahe Psychiatrie West/Suedwest, Leipzig, Germany
†Department of Psychiatry, Bezirksklinikum, University of Regensburg, Regensburg, Germany
‡Section for Geriatric Psychiatry, University of Heidelberg, Heidelberg, Germany
§Eisai GmbH, Frankfurt, Germany
¶Eisai Co Ltd, London, UK

Address for correspondence: Professor Ruediger Mielke, University of Cologne, Herbert-Lewin-Str. 2, D-50931 Köln, Germany. Tel.: +49-221-4704919; Fax: +49-221-4703153; email: r.mielke@uni-koeln.de

Key words: Alzheimer’s disease – Donepezil – Memantine – Nootropics – Observational study – Post-marketing surveillance

ABSTRACT

Objective: This open-label, prospective, observational, Post-Marketing Surveillance (PMS) study assessed the efficacy and safety of donepezil in patients who had been switched from therapies currently used in Germany to treat Alzheimer’s disease (AD), such as memantine and nootropics, due to insufficient efficacy or poor tolerability. A treatment-naïve population was included as a comparator.

Research design and methods: Patients with AD were treated with donepezil and observed for a period of approximately 3 months. A cognitive assessment was made using the Mini-Mental State Examination (MMSE). Quality of life (QoL) was assessed by the investigators who answered the question ‘How did therapy with donepezil influence the QoL of the patient and/or his family over the observation period?’ and was graded using three ratings: improved/unchanged/worsened. Adverse events (AEs) were also monitored.

Results: A total of 913 patients entered the study (mean ± SD MMSE score 18.03 ± 5.34). Efficacy assessments were analyzed for three groups: an overall group of patients who had received any form of prior AD drug therapy...
Efficacy of donepezil in AD patients switched from memantine or nootropics

Introduction

The number of dementia cases in the European Union is currently estimated to range from 3.25 to 5.36 million and about 50–70% of these are diagnosed as Alzheimer’s disease (AD). During the past 50 years, advances in modern medicine have resulted in an increase in life expectancy, and this trend is projected to continue until the end of the 21st century. As AD is primarily a disease of middle-to-old age, the number of cases is likely to increase dramatically. Thus, effective management of this condition is important now and for the future.

It is widely recognized that degeneration of cholinergic neurons in the brain is a major contributor to the progressive decline in cognition and ability to function in daily life that is typically observed in AD patients. This cholinergic loss may also play a role in the behavioural changes seen in AD. Consequently, pharmacologic treatment has focused on restoration of cholinergic function to improve the clinical symptoms of the disease. Cholinesterase inhibitors (ChEIs) are a class of drugs that have been widely investigated for the treatment of AD. These compounds act by inhibiting acetylcholinesterase, the enzyme which breaks down acetylcholine in the synaptic cleft; the result of this inhibition is enhanced cholinergic neurotransmission.

The first ChEI to be approved, tacrine, has been limited in its use due to hepatotoxicity. Donepezil hydrochloride is considered to be the first practically usable ChEI to be licensed for AD, and is now approved for the symptomatic treatment of mild to moderate AD (United States product labelling) or mild to moderately severe AD (European product labelling) in over 80 countries. Efficacy, safety and tolerability of donepezil in patients with mild to moderately severe AD have been widely demonstrated in placebo-controlled clinical trials in open-label studies with patient populations similar to those seen in everyday clinical practice and in a Post-Marketing Surveillance (PMS) observational study in Germany. In addition to these studies in mild to moderate AD patients, donepezil has been shown to improve global functioning, cognition and behaviour above baseline levels and to slow the rate of decline in activities of daily living in a placebo-controlled trial in patients with moderate to severe AD. Subanalyses of this study have shown similar efficacy in the moderate (Mini-Mental State Examination [MMSE] score 10–17) and more advanced (MMSE score 5–12) AD cohorts enrolled. The benefits achieved with donepezil therapy in treating AD patients have also been found in studies to have a positive impact on both caregiver burden and societal costs of AD.

Memantine hydrochloride is a derivative of the anti-influenza drug amantadine. It has been used in Germany since 1989 to treat dementia and has recently been licensed in the European Union and United States for the specific treatment of moderately severe to severe AD. Memantine acts as a non-competitive (open-channel) antagonist of the N-methyl-D-aspartate (NMDA) receptor. Unlike the ChEIs, which are directed at restoring a deficit that is well established in the pathology of AD, the role of memantine’s mechanism of action in treating the specific pathology of AD – especially its role in symptomatic improvement – is less well defined. In a 6-month monotherapy trial of patients with MMSE scores of 3–14, memantine-treated patients generally showed less decline than placebo-treated patients, rather than persistent improvement above baseline, on measures of cognition, global function and activities of daily living.

In Germany, in addition to the proven therapies for AD (memantine and ChEIs), nootropics such as ginkgo biloba, nicergoline, nimodipine and piracetam are often prescribed. A variety of mechanisms have been proposed to account for the observed benefits of such nootropic agents in patients with cognitive impairment and dementia. These principally focus on increasing cerebral blood flow (ginkgo biloba, piracetam, nicergoline) and oxygen and glucose use in the brain (piracetam, nicergoline). Additional mechanisms such as modification of neurotransmitter systems (ginkgo biloba) and readdressing the age-related disturbances in calcium homeostasis (nimodipine) have also been suggested. However, there is no common agreement on how these drugs actually work and robust data of their efficacy from randomized controlled trials are lacking.
Patients and methods

Study design

This was a PMS analysis of combined results from two open-label, prospective, observational cohort studies in patients who had been diagnosed with AD (MMSE score 0–30). Study protocols were identical, and the study populations were representative of AD patients, thus allowing data collected to be pooled. These studies were undertaken mainly by office-based neurologists, psychiatrists and other specialists in geriatrics between June 1999 and February 2000. Since the aim of both studies was to collect information on the routine (prescription) use of donepezil for the treatment of AD, there were no inclusion or exclusion criteria for participation in either study, aside from that detailed in the current labelling for donepezil. The length of the observation period for patients in both studies was approximately 3 months. The studies were registered with the German regulatory authority (BfArM) and the National Association of Social Health Insurance (SHI)-Accredited Physicians (‘Kassenärztliche Bundesvereinigung’ [KBV]). Independent Ethics Committee approval was not required for PMS studies at the time of this investigation. Data were collected in a standardized manner and recorded on case-report forms, which allowed for subsequent coding and analysis. Recording and storage of data were conducted according to data protection regulations.

The physicians conducting this study were paid to document the observations on patients they enrolled. Donepezil was prescribed to patients in the usual manner and was not paid for by the study sponsor. Studies of this nature are designed to monitor real world, clinical use of marketed drugs and are required by German regulatory authorities.

Patient population and switching criteria

Patients enrolled in this study were either treatment naive or, in the majority of cases, were being treated with memantine and/or a nootropic agent (ginkgo biloba, nicergoline, nimodipine or piracetam). Small numbers of patients also received other therapies, e.g. rivastigmine. Also included in the other medications category were agents such as antithrombotics, vasodilators and calcium channel blockers, used to manage cardiovascular conditions that may exacerbate AD and also central nervous system drugs such as tranquilizers, used to manage behavioural problems associated with AD. As part of normal clinical practice, the treating physician assessed whether a patient who was already receiving AD medication required an alteration to their medication. The criteria for switching were insufficient efficacy, poor tolerability or a request from a patient or caregiver to change medication. Other factors that influenced switching were more convenient dosing regimens or titration schedules and the potential for an effect on disease progression. The protocol stated that the patient and/or physician must give a valid reason for the patient to switch to donepezil in order to enrol in the study. It should be noted that at the time of the study, memantine had been approved in Germany for approximately 18 years as a general anti-dementia treatment and was in reasonably widespread clinical use. It had not yet received approval specifically for moderately severe to severe AD.

Donepezil treatment

Dosing of donepezil was in accordance with the approved product labelling in Germany. Initially, patients received open-label donepezil 5 mg once daily. After at least 1 month, the dosage of donepezil could be increased to 10 mg once daily based on clinicians’ judgment of tolerability and efficacy. The dose could be changed during the observation period at the discretion of the investigator. All dose changes were recorded.

Efficacy and tolerability assessments

At baseline, the demographic characteristics, medical history, prior and current treatments for AD, other current medications and comorbid illnesses were recorded.

The patient population was divided into three groups for efficacy assessment:

1. N+: All patients who were receiving a defined dementia therapy, i.e., memantine or rivastigmine, or a nootropic agent (ginkgo biloba, nicergoline, nimodipine, piracetam) or a medication prescribed to manage AD risk factors (e.g. cardiovascular agents) or behavioural symptoms (e.g. tranquilizers) at baseline.

2. M+: A subgroup of patients from the N+ group who were being treated with memantine only at baseline.
3. N–: Untreated patients.

To evaluate efficacy, patients were assessed at baseline and after 3 months using the MMSE. The MMSE is probably the most widely used formal cognitive assessment tool in routine clinical practice. It is a 30-point scale used to assess the patient’s cognitive function in the domains of a person’s orientation to time and place, recall ability, short-term memory and arithmetic ability. Scores range from 0 to 30, and lower scores indicate more severe impairment. It was chosen because of its practicality and physicians’ familiarity with its use.

An assessment of patient QoL was obtained at the end of the observation period using global clinical judgments. Investigators answered the question: ‘How did therapy with donepezil influence the quality of life of the patient and/or his family over the observation period? Was it improved, unchanged, or worsened?’

At the end of the observation period, supportive information was obtained by the investigator using separate global clinical judgments of efficacy and tolerability. Investigators rated the efficacy of donepezil as ‘very good’, ‘good’, ‘satisfactory’, ‘moderate’, ‘no effect’ and ‘not assessable’. This is in effect, a modified Clinician’s Global Impression of Improvement (CGI-I) scale. Similarly, the tolerability of treatment with donepezil was categorized as ‘very good’, ‘good’, ‘moderate’ or ‘unsatisfactory’.

Safety analysis was performed on all patients receiving donepezil by physicians actively asking both patients and caregivers if any adverse events (AEs) had occurred. AEs were recorded on case-report forms and classified according to the World Health Organization, Adverse Reaction Terminology (WHO-ART) preferred term classification. Severe AEs were also recorded, and their possible relationship to donepezil treatment was assessed by investigators. An AE was defined as severe in line with accepted regulatory guidelines, i.e., if it led to death, hospital admission, lasting damage to health, congenital abnormalities, was life-threatening, or was medically or significantly important.

Data analysis

Due to the observational nature of this study, data were not always available for the total patient population. Therefore, descriptive statistics were applied to the data available for the population enrolled at baseline, i.e., the evaluable population. Adverse events are reported for the entire safety population, defined as any enrolled patient who received at least one dose of donepezil. Descriptive statistical analyses of the MMSE and judgments of global efficacy, QoL and tolerability were carried out only for those cases for which data were available. With regards to the change in MMSE scores from baseline to study end, statistical analysis was carried out using the t-test, where p-values of ≤ 0.05 were considered significant. No specific action was taken for missing values at either baseline or the 3-month evaluation time point.

The efficacy of donepezil was evaluated according to mean (± SD) changes in the total score on the MMSE. A responder analysis calculating percentage of patients showing an improvement in total MMSE score of ≥ 3 or ≥ 6 was also carried out. For global judgment of efficacy, percentages rated in each of the categories were calculated.

Results

Overall, data were collected from 913 AD patients in this PMS study (650 patients from one study and 263 from the other). Of these 913 patients, 709 had received prior therapy with memantine and/or nootropics (N+ group). The subgroup that received prior memantine therapy (M+) comprised 111 patients. The N+ group also included 209 patients who received ginkgo biloba, 71 who received nicoergoline, 33 who received nimodipine, 329 who received piracetam and 119 who were treated with other therapies, including five patients who took rivastigmine. At baseline, 556 patients were receiving one medication only for AD and 153 patients were receiving more than one therapy for AD (2 therapies, n = 124; 3 therapies, n = 24; 4 therapies, n = 3; 5 therapies, n = 1 or 6 therapies, n = 1). The main reasons for physicians switching patients to donepezil therapy were for insufficient efficacy of existing therapy (87% of patients) and poor tolerability (80.9%). A total of 204 patients were treatment naive. Concurrent psychotropic medications with possible anticholinergic potential that may have an effect on the donepezil treatment included amitriptyline, doxepin, pipamperone, melperone and mirtazapine. The baseline mean MMSE score in the evaluable patient population (n = 906) was 18.03 ± 5.34, and for the N+, M+ and N– groups were 18.32 ± 5.36 (n = 704), 16.62 ± 5.60 (n = 109) and 17.02 ± 5.15 (n = 202) respectively. Other patient baseline demographics are shown in Table 1.

The mean observation period for patients receiving donepezil was 14.6 weeks. For the patients with MMSE scores recorded at the end of the observational period (n = 860), donepezil improved MMSE scores by a mean of 2.21 ± 3.47 points across all groups (p = 0.0001). Patients in all groups (N+, M+ and N–) showed similar improvements in MMSE scores. In the N+ group, scores improved by 2.11 ± 3.36 points (n = 664; p = 0.0001), in the M+ group by 2.34 ± 3.84 points (n = 107;
Efficacy of donepezil in AD patients switched from memantine or nootropics
Klinger et al.

Patients receiving a constant dose of 5 mg donepezil \( (n = 409) \) showed an improvement of 2.24 ± 3.22 points, while those receiving 10 mg for at least part of the trial (mean duration 7 weeks; \( n = 406 \)) improved by 2.28 ± 3.62 points. Patients in the N+, M+ and N– groups showed similar improvements on both the 5 mg and 10 mg dosing regimens.

Irrespective of the type of AD therapy that patients had received, when switched to donepezil the investigators’ judgment of global efficacy was similar. Efficacy was judged ‘very good’ or ‘good’ in 59.5% of the total population, 58.6% of the N+ cohort, 58.2% of the M+ cohort and 62.4% of the N– cohort.

Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, male/female, % of patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean age, years ± SD (range)</td>
<td>73.4 ± 8.6 (33–96)</td>
<td>912</td>
</tr>
<tr>
<td>Mean height, cm ± SD (range)</td>
<td>167.7 ± 7.7 (145–196)</td>
<td>888</td>
</tr>
<tr>
<td>Mean weight, kg ± SD (range)</td>
<td>69.6 ± 10.7 (39–115)</td>
<td>886</td>
</tr>
<tr>
<td>Mean AD duration, months ± SD (range)</td>
<td>31.2 ± 23.3 (2–192)</td>
<td>619</td>
</tr>
<tr>
<td>MMSE ± SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total population</td>
<td>18.03 ± 5.34</td>
<td>906</td>
</tr>
<tr>
<td>N+ cohort</td>
<td>18.32 ± 5.36</td>
<td>704</td>
</tr>
<tr>
<td>M+ cohort</td>
<td>16.62 ± 5.60</td>
<td>109</td>
</tr>
<tr>
<td>N– cohort</td>
<td>17.02 ± 5.15</td>
<td>202</td>
</tr>
<tr>
<td>Received any prior drug therapy for AD, % of patients</td>
<td>77.7</td>
<td>709</td>
</tr>
<tr>
<td>Received memantine therapy for AD, % of patients</td>
<td>12.2</td>
<td>111</td>
</tr>
<tr>
<td>Comorbid medical condition of any kind, % of patients</td>
<td>60.2</td>
<td>550</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>34.3</td>
<td></td>
</tr>
<tr>
<td>Endocrine/metabolic</td>
<td>12.3</td>
<td></td>
</tr>
<tr>
<td>Psychiatric</td>
<td>11.9</td>
<td></td>
</tr>
<tr>
<td>Neurologic</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Concomitant medication of any kind, % of patients</td>
<td>63.2</td>
<td>577</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>8.9</td>
<td>81</td>
</tr>
<tr>
<td>Nervous system</td>
<td>11.6</td>
<td>106</td>
</tr>
</tbody>
</table>

AD = Alzheimer’s disease; MMSE = Mini-mental state examination

Due to the nature of this post-marketing, observational study data for all parameters were not obtained at baseline for all 913 patients enrolled. No action was taken to correct for missing values.
Quality of life was judged ‘improved’ in 70.0% of the total patient population ($n = 892$), 68.7% of the N+ cohort ($n = 691$), 72.1% of the M+ cohort ($n = 111$) and 74.1% of patients in the N– cohort ($n = 201$) (Figure 4). In the investigators’ global judgment of tolerability, the tolerability of donepezil was judged ‘very good’ or ‘good’ in 93.5% of the total patient population, in 93.2% of the N+ cohort, 95.5% of

**Figure 3.** Investigators’ global judgment of efficacy in the evaluable patient population, in the subgroups of patients who had received prior memantine or nootropic therapy (N+) or prior memantine therapy only (M+) and in patients who were treatment naive (N–)

**Figure 4.** Quality of life, as judged by investigators, following donepezil therapy in the evaluable patient population, in the subgroups of patients who had received prior memantine or nootropic therapy (N+) or prior memantine therapy only (M+) and in patients who were treatment naive (N–)

**Figure 5.** Investigators’ global judgment of tolerability in the total evaluable patient population, in the subgroups of patients who had received prior memantine or nootropic therapy (N+) or prior memantine therapy only (M+) and in patients who were treatment naive (N–)
the M+ cohort and in 94.6% of the N– cohort (Figure 5).

Donepezil was well tolerated in all treatment groups. AEs were reported in 85 patients (9.3%) out of the total patient population of 913. A total of 59 patients discontinued the study prematurely. Of these 32 gave AEs as reason for discontinuation, three died and seven reported no response. The most common AEs reported were diarrhoea, vomiting, nausea and marked restlessness (Table 2). Of patients reporting AEs who had a dosage increase of donepezil from 5 mg/day to 10 mg/day, 13 (3.1%) reported AEs. Fourteen patients (1.5%) reported severe AEs following donepezil treatment. The most commonly reported severe AEs were general disorders in the body as a whole (four patients), psychiatric disorders (three patients), central and peripheral nervous system disorders (two patients) and gastrointestinal disorders (two patients). For the nine patients where such data were available, severe AEs were considered to be ‘possibly related’ to donepezil therapy in one patient and ‘probably related’ to donepezil therapy in two patients.

Discussion

The results from this PMS, open-label, prospective, observational study show that AD patients who are either not tolerating or are insufficiently treated with memantine or nootropics drugs commonly prescribed for AD, have improved cognitive function as measured by the MMSE and QoL as judged by the treating physician when switched to donepezil. The responses observed in patients with prior treatment were similar in magnitude to treatment-naive patients; therefore, prior medication with other therapies did not seem to affect the response to donepezil treatment. The beneficial effects of donepezil treatment, as demonstrated in placebo-controlled trials of up to 1 year duration, were clearly evident in this ‘real world’ setting.

Overall, the AD patients in this study were typical of those seen in routine clinical practice in Germany and, in most respects, had a similar demographic profile to populations who had taken part in earlier placebo-controlled trials with donepezil and in another open-label, observational, German PMS study. However, although the percentage of patients in this study with co-morbid illnesses and concomitant medications was similar to that from another German PMS study, these percentages were somewhat lower than previously observed in other open-label and placebo-controlled studies of donepezil. This is likely due to the unstructured nature of the data collection for these parameters in this observational study.

The protocol was designed to allow physicians to choose from several different reasons to explain why a patient should be switched to donepezil from their existing therapy. These reasons included insufficient efficacy and poor tolerability of their current treatment and a patient or caregiver requesting the change. Insufficient efficacy of existing therapy (87% of cases) and poor tolerability of existing therapy (80.9% of cases) were the main reasons given, with some cases stating both of these as leading to the decision to switch therapies. Therefore, all these patients were considered by the physician to require a change of therapy, and this change reflected normal clinical practice and was not made as a result of study participation. It is unclear why such a high percentage of patients were stated to have poorly tolerated their current medication as a reason for switching therapies, given that the majority of patients were taking ginkgo biloba and piracetam, compounds with recognized excellent tolerability profiles. One possible explanation for this may be selection bias, as patients with good tolerability towards these agents were not considered for a switch. Whatever the case, in the 8-month period of recruitment for this study, over 700 patients were considered by their physicians as not being optimally treated by their existing AD therapy, including memantine and nootropics. The relatively large size of this sample of patients whose physicians judged their treatment not sufficiently effective enables some meaningful conclusions to be drawn from this observational study.

The mean 2.21 point improvement from baseline in total MMSE scores for the evaluable population confirms that the cognitive benefits of donepezil observed in controlled studies can also be measured in routine clinical practice. The similar magnitude of improvement on the MMSE for all three groups demonstrates that patients who have been judged to have an insufficient response to other AD therapies respond to donepezil with a similar efficacy to that of treatment-naive patients. Moreover, the magnitude of the donepezil response was not affected by the severity of the disease as patients in the memantine group had lower baseline MMSE scores than treatment naive patients. Since nearly 50%

Table 2. Adverse events occurring in more than 0.5% of the total patient population (n = 913)

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>Number of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>22 (2.4)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>12 (1.3)</td>
</tr>
<tr>
<td>Marked restlessness</td>
<td>10 (1.1)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>10 (1.1)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>6 (0.7)</td>
</tr>
<tr>
<td>Aggressiveness</td>
<td>6 (0.7)</td>
</tr>
<tr>
<td>Sleep disturbance</td>
<td>6 (0.7)</td>
</tr>
<tr>
<td>Sleeplessness</td>
<td>5 (0.5)</td>
</tr>
<tr>
<td>Headache</td>
<td>5 (0.5)</td>
</tr>
</tbody>
</table>
of patients who responded to donepezil achieved a \( \geq 3 \)-point improvement on the MMSE and 13% a \( \geq 6 \)-point improvement, it is clear that the cognitive effects of donepezil can be substantial in some patients. In line with the cholinergic hypothesis, this likely reflects the effectiveness of a cholinergic-enhancement therapy in providing symptomatic relief in AD compared with therapies with different, less well defined modes of action. The changes in MMSE score are considered to be meaningful since changes in MMSE of only one point have been associated with substantial improvements. Patients on 10 mg donepezil have been shown in a meta-analysis to do better than those on the 5 mg dose. In this study, the improvements from baseline MMSE scores were similar over the course of the study for the 5 mg and 10 mg doses of donepezil in the total population and in the three subgroups. This is probably due to the relatively short duration of the study (mean observation period of 14.6 weeks) and the variability of the time taken to increase the dose to 10 mg (mean time of 7.6 weeks for first dosage increase), resulting in relatively short times on 10 mg donepezil (mean time of 7 weeks) before the final assessment. In addition, some patients were returned to the 5 mg dose because they did not tolerate the 10 mg dose.

The clinical judgment of donepezil’s global efficacy was rated by the investigator as ‘very good’ or ‘good’ in nearly 60% of the total population, and comparable efficacy was noted in the three groups. On switching to treatment with donepezil, the overall tolerability of donepezil was judged ‘very good’ or ‘good’ in over 90% of patients, and comparable tolerability was noted in all three groups. These results are notable because they represent judgments made in routine clinical practice in a setting where other AD treatments have been assessed as not clinically effective and, as such, they support the results of randomized, double-blind, placebo-controlled trials.

Although there is an ongoing controversy about measuring QoL in patients with dementia, and a lack of reliable and validated scales, there is a continuing need to try to assess QoL for both patients and caregivers in routine clinical settings that reflect daily life. Due to the lack of insight into their own condition, it is common for QoL assessments of dementia patients to be made by proxy, either by the caregiver or the investigator. In addition, it is increasingly recognized that due to the highly dependent nature of the relationship between an AD patient and their caretaker, the QoL of the caretaker should also be taken into account when fully assessing the impact of a treatment.

Quality of life assessments of patient well-being have been carried out in the pivotal clinical trials with donepezil, using patient-rated, non-validated scales, and improvements in favour of donepezil were noted at some time points between donepezil-treated patients and those who received placebo. However, extensive inter- and intra-patient variability, and the fact that the instrument used lacked sensitivity, may have affected the results. A subanalysis of Australian AD patients from a large multinational experience study into the efficacy of donepezil showed baseline scores were significantly improved by donepezil for several items on the Australian QoL scale (physical senses, social relationships and independent living).

In this study, a pragmatic approach was taken with the investigators answering a single question: ‘How did therapy with donepezil influence the quality of life of the patient and/or his family over the observation period?’, offering three possible outcomes: improved/unchanged/worsened. Following donepezil therapy, QoL was judged to be improved by the investigator in more than two-thirds of cases. Although, for reasons outlined above, this was not a comprehensive investigation into patient and caregiver QoL, this assessment gives an impression of the impact an effective therapy, such as donepezil, can have on the daily lives of AD patients, their caregivers and families.

As expected from the placebo-controlled, double-blind and open-label trials, donepezil was well tolerated in this study population, with the incidence of reported AEs being notably low (9.3% of patients). Predictably, the most common AEs were cholinergic-related side-effects such as nausea, diarrhoea and vomiting. The incidence of these AEs were noted in < 3% of patients (Table 2) and were considerably lower than recorded in controlled trials. However the threshold for AE reporting is likely to be much lower in a controlled trial than in a naturalistic study of this kind.

In order to reflect the ‘real world’, observational characteristics of this study, efficacy measures were chosen that were both familiar to the physician (MMSE) and straightforward (global clinical judgments on efficacy and tolerability). The categories used in the global clinical judgments on efficacy and tolerability measurement reflect the simple assessments used in the real-life environment, and are not dissimilar to a Likert-type scale such as that used in the CGI-I or the Clinician’s Interview Based Impression of Change (CIBIC) measurements. In this study, the MMSE, an objective measure, was used as the primary efficacy measure, while the global assessment, a subjective measure, was used as a supportive parameter.

It must be recognized that there are limitations to an observational PMS study, as such investigations are designed to gather information on a marketed drug as it is used in routine clinical practice. In the PMS study...
setting, physicians are not blinded to their patients’ treatment. As such, there is the possibility of bias in the assessments used, whether they are objective or subjective. Additionally, care and attention received by the patient by virtue of participating in a study together with a placebo effect may have some influence on the results. Moreover, in switch studies investigator bias towards a new treatment should also be taken into account. Although the use of a placebo-controlled arm would have gone some way to reducing these limitations, this is not possible in a ‘real-life’ study such as a PMS. Nonetheless, PMS studies are routinely done in Germany and are in fact required by German regulatory authorities. This is because they provide a structured mechanism for gathering both efficacy and safety data as drugs gain routine use by a wide range of patients and practitioners, and thus have a value that complements data from randomized, double-blind, placebo-controlled, clinical trials.

Another criticism of this investigation may be that it is short. Three months was chosen as the minimum period of study since this enables the assessors to establish first impressions of efficacy without compromising the quality of the data due to attrition that can occur with longer trials in AD.

As one might expect from the nature of the study, the patient population was highly heterogeneous. Therefore, to reduce the potential for false outcomes from this population, extensive statistical tests were not performed on the data. As with all switching studies there is some bias in the study design that needs to be taken into account. By the very nature of a switch study the patient population is biased towards the drug they are switched to because they did not have a sufficient response to or tolerate their previous medication. In this study, the similar magnitude of the responses on the MMSE of treatment-naive and previously treated patients following donepezil therapy suggests that any bias in the switched population was minimal.

Despite their limitations, PMS studies have value in that they provide physicians with information gained from a real-life setting. In this case it may provide some guidance to a physician on the expected outcome of changing a patient’s therapy from a nootropic or memantine to a ChEI. It should be remembered that PMS studies are not intended to be a definitive judgment on efficacy but rather to emulate a real-life situation of usage of the drug under observation.

It is common clinical practice in Germany to treat AD patients with proven (memantine and ChEIs) and unproven (nootropics) therapies, although it should be remembered, as noted above, that at the time of this study memantine had not yet received regulatory approval specifically for AD. While it is good clinical practice to assess efficacy and tolerability of therapies, and to change therapies when appropriate, premature switching should be avoided. In a study with donepezil, patients who lacked clear clinical benefit during 12–24 weeks of initial treatment went on to experience cognitive, behavioural and functional benefits when therapy was continued for a further 12 weeks when compared to patients switched to a placebo37. Thus, changing therapies should be exercised with care and decisions about a therapy’s efficacy should not be made on the basis of the MMSE score alone. At present, there is limited research to guide the clinician switching a patient from a therapy that is ineffective or not tolerated. To our knowledge, this is the first study to report the benefits of switching to a ChEI from a different class of drug: in particular, we have demonstrated benefits in switching from memantine, an NMDA receptor antagonist, to donepezil.

**Conclusions**

Our results clearly show that patients who are not sufficiently responding to, or are unable to tolerate, memantine or the unproven nootropic therapies, respond favourably to donepezil over a period of at least 3 months.

**Acknowledgements**

This study was funded by Eisai Co., Ltd. and Pfizer Inc. The authors acknowledge PPS International for assistance with manuscript preparation.

The authors acknowledge that data from this manuscript have been presented at the following meetings:

References


CrossRef links are available in the online published version of this paper:
http://www.cmrojournal.com
Paper CMRO-2876 3, Accepted for publication: 21 March 2005
Published Online: 14 April 2005
doi:10.1185/030079905X436688