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An Observational Clinical Study of the Efficacy and Tolerability of Donepezil in the Treatment of Alzheimer's Disease

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Key Words
Alzheimer's disease · Donepezil · Observational study · Post-marketing surveillance · Acetylcholinesterase inhibitor · Cognition · Activities of daily living

Abstract
An open-label, observational Post-Marketing Surveillance (PMS) study was undertaken in Germany to examine the efficacy and tolerability of donepezil in routine clinical practice. Alzheimer's disease (AD) patients were treated with donepezil (5 or 10 mg once daily) and observed for a period of approximately 3 months. Study assessments included the Mini-Mental State Examination (MMSE), the Nurses' Observation Scale for Geriatric Patients (NOSGER), and adverse events (AEs). A total of 2,092 patients (mean age 73.0 years; mean ± SD MMSE score 17.8 ± 5.8) were included in the efficacy assessments. MMSE and NOSGER scores showed statistically significant improvements in the total patient population and in the subpopulations with severe AD or AD with concomitant Parkinsonian symptoms (ADPS cohort). AEs were reported in a total of 12% of patients and were mostly due to peripheral cholinergic effects. In this observational PMS study, donepezil was shown to be an effective and well-tolerated therapy in the overall patient population, in patients with severe AD, and in the ADPS cohort.

Introduction

Alzheimer's disease (AD) is a progressive debilitating disorder estimated to affect some 5–10% of people over 65 years old and as many as 50% of those over 85 years of age [1]. AD is characterised by degeneration of cholinergic innervation in the cerebral cortex, and numerous trials have evaluated cholinesterase (ChE) inhibitors as potential therapeutic agents [2]. The first two widely used ChE inhibitors were physostigmine and tacrine. In clinical trials with these compounds, undesirable cholinergic side effects were reported [3–7]. The use of tacrine was also associated with dose-limiting hepatotoxicity [3, 8]. In addition, administration of these two drugs requires more than once-daily dosing [9].

Donepezil hydrochloride (Aricept®) is a potent, reversible, and highly selective inhibitor of acetylcholinesterase (AChE), and, as a piperidine-based agent, it is chemically distinct from other ChE inhibitors [10–14]. Donepezil has

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a favourable pharmacokinetic profile, eliminating the need for dose adjustment in special populations of patients. Comparable pharmacokinetics have been demonstrated in the young and elderly [15], and renal or hepatic impairment does not affect the pharmacokinetics of single-dose oral donepezil 5 mg [16, 17]. Renal impairment also does not affect the pharmacokinetics of multiple oral doses of 5 mg donepezil [18]. Plasma concentrations of donepezil and AChE inhibition are increased in mild to moderately impaired hepatic patients, following multiple oral dose administration of 5 mg donepezil, however treatment was safe and well tolerated in this population [19]. Furthermore, the long dose-independent plasma half-life of donepezil [20] allows once-daily dosing.

The efficacy and good tolerability of donepezil in treating the symptoms of AD in patients with mild to moderately severe disease have been demonstrated in Phase II and Phase III placebo-controlled trials of up to 6 months' duration [21–24]. More recently, two extended placebo-controlled trials have reported additional and more sustained benefits. The first of these reported benefits with donepezil on global function, cognition and activities of daily living (ADLs) over a period of one year [25]. In the second study, the likelihood of patients retaining functional capacity over one year was significantly increased with donepezil 10 mg/day [26]. In addition, a long-term, open-label extension study demonstrated that donepezil was well tolerated and provided benefits in cognition and global function that continued for up to 2.8 years in patients remaining on treatment, compared to historical cohorts of untreated AD patients [27].

These studies were designed to establish the efficacy and tolerability of donepezil and therefore, like all such trials, were tightly controlled in order to limit the potentially confounding effects of factors other than the test treatments. In particular, patients with a range of comorbid medical conditions and those who were receiving certain concomitant medications were excluded. After approval, regulatory authorities often require additional information on the efficacy, tolerability, and safety of a drug in routine medical practice. One way to meet this requirement appropriately is to conduct Post-Marketing Surveillance (PMS) studies ('studies of use') in larger cohorts of patients. In these open-label observational studies, patients are treated with the agent under examination at the discretion of their physician, and are only excluded from the study if the agent is contraindicated.

This paper reports on the combined results of two PMS studies, including clinical efficacy and safety information. These studies followed the recommendations for performing 'studies of use' set forth by the German Federal Institute for Medicines and Medicinal Products (BfArM, November 1998 [28]). In addition, the paper reports on an exploratory post-hoc analysis that was performed in 2 subpopulations of patients: with severe AD, and AD with concomitant Parkinsonian symptoms (ADPS cohort).

Methods

Study Design

Donepezil has been used in clinical practice in Germany since October 1997. This was a Post-Marketing Surveillance (PMS) analysis of combined results from two open-label, prospective, observational cohort studies undertaken mainly by office-based neurologists, psychiatrists, and other specialists in geriatrics across Germany between October 1997 and May 1999. A total of 580 investigators participated. 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, apart from the current labelling for donepezil. The length of the observation period for patients from both studies was to be approximately 3 months. The studies were registered with the German regulatory authority (BfArM) and the National Association of Social Health Insurance (SHI)-Accredited Physicians ('Kassenaerztliche Bundesvereinigung' [KBV]). Recording and storage of data were conducted according to data protection regulations.

Donepezil Treatment

In this naturalistic PMS study, no specific dosing regimens were stipulated. Dosing was to follow the approved German labelling of Aricept®, that is, 5 mg once daily with the possibility of increasing to 10 mg once daily after 4 to 6 weeks, based on clinicians' judgement of tolerability and efficacy.

Assessments

The following information was recorded at baseline: demographic characteristics, medical history, prior and current treatments for AD, other medications, and concomitant illnesses (according to ICD-10 classification). To evaluate efficacy, patients were assessed at baseline and after 3 months using the Mini-Mental State Examination (MMSE) [29] and the Nurses' Observation Scale for Geriatric Patients (NOSGER) [30, 31].

The MMSE is the preferred cognitive assessment tool in routine clinical practice [32]. It is a 30-point scale used to assess patients' cognitive function across the dimensions of orientation, registration, attention and calculation, recall, and language, and provides an estimate of the severity of cognitive impairment. Scores on the MMSE range from 0 to 30, and lower scores indicate more severe impairment. The NOSGER is a 30-item questionnaire completed by the caregiver to assess the patient with regard to the dimensions of memory, instrumental activities of daily living (IADLs), basic ADLs, mood, social behaviour, and disturbing behaviour, each of these dimensions consisting of five items. For each individual item, there are five possible answers to describe the frequency of a specific behaviour ('all the time', 'most of the time', 'often', 'sometimes', 'never'). These answers are scored in a range from 1 to 5, thereby yielding a total score for each dimension of 5 to 25. Higher scores

indicate more severe disturbance or impairment. Thus, clinical improvement will be reflected by a decline (i.e. a negative change) in dimension scores.

At the end of the observation period, supportive parameters were obtained by the investigator using separate global clinical judgements of efficacy and tolerability. For efficacy assessments, investigators rated the symptoms of AD as, 'markedly improved', 'improved', 'unchanged', 'worse', or 'markedly worse'. Similarly, the tolerability of treatment with donepezil was categorised as 'very good', 'good', 'moderate', or 'unsatisfactory'.

All AEs reported during the study were recorded and categorised according to the WHO-ART (World Health Organisation, Adverse Reaction Terminology) preferred terms and body system classification. All Serious AEs (SAEs) were also listed and described, and assessments (by the investigator) of their possible relation to donepezil treatment were made.

Data Analysis

A descriptive analysis was performed on both efficacy and tolerability data. All data analyses were performed on the respective 'Observed Cases' (OC) population, which included those patients for whom the data in question (e.g. MMSE at baseline and at the end of the observation period) were available. The respective patient numbers are found in the Results section. No specific action was taken for missing values.

The efficacy of donepezil was evaluated according to mean (± SD) and median changes in the total score on the MMSE, as well as in the separate dimension scores on the NOSGER questionnaire. A responder analysis for the total MMSE score was undertaken by dividing all patients completing the observation period into quartiles according to the degree of change in total MMSE score. This provided information on the respective MMSE changes in each quartile of the evaluable patient population.

A subgroup analysis was also undertaken to assess responses to donepezil treatment relative to baseline cognitive impairment, categorised according to the baseline MMSE total score: mild = 19–30 points; moderate = 11–18 points; severe = 0–10 points. Changes in MMSE total score and separate NOSGER dimension scores were analysed for each of these three patient subgroups. A subgroup analysis of treatment response also considered individual NOSGER items such as behavioural problems and basic ADL deficiencies, analysing the frequency of improvement (or worsening) of patients with these particular characteristics during treatment.

In the evaluation of tolerability, subgroup analyses were performed for patients with any history of cardiovascular disease, including bradycardia. In addition, analyses of any AEs occurring in patients taking concomitant beta blockers or selective serotonin reuptake inhibitors (SSRIs) during donepezil treatment were also performed and the appropriate relative risks were evaluated.

Results

Patients

A total of 2,092 patients were included in the efficacy evaluation of donepezil in this PMS study (1,649 from one study and 443 from the other). In the analysis of AEs, an additional two patients were included, resulting in a total safety population of 2,094 patients. The characteristics of the patients and mean MMSE and NOSGER scores at baseline are shown in table 1. Out of 2,073 patients for whom diagnostic information was available, 600 (28.9%) had a new diagnosis of AD, while 1,473 (71.1%) had pre-existing AD. Nearly all (>95%) patients enrolled were outpatients. In patients with a prior diagnosis, the mean (± SD) duration of AD was 31.8 ± 24.3 months (range 1–216). The majority of patients (59.0%) had co-morbid illnesses, most of which were cardiovascular (31.2%), endocrine/metabolic (13.1%), psychiatric (13.0%) and neurologic (9.4%) disorders. A comparable proportion of patients (56.5%) were on concomitant medications, especially cardiovascular and central nervous system agents (30.5% and 29.2%, respectively). Peripheral vasodilators were taken by 13.4% of patients. Out of the entire group of 2,092 patients enrolled, 42.9% had received prior AD therapy (42.0% drug therapy, 3.7% other AD treatments). The most common medications were psychoanaleptics (classification N06 according to the Anatomical Therapeutic Chemical (ATC) classification, including antidepressants and psychostimulants/nootropics), which were taken by 16.0% of patients.

Table 1. Baseline patient characteristics

Gender, male/female, % of patients	39.2/60.8
Mean age, years (range)	73.0 (27.0–100.0)
Mean height, cm (range)	167.3 (145.0–196.0)
Mean weight, kg (range)	69.2 (39.7–115.0)
Mean baseline MMSE total score ± SD	
(n = 1,920)	17.8 ± 5.8
Mild (MMSE 19–30), n (%)	953 (49.6)
Moderate (MMSE 11–18), n (%)	733 (38.2)
Severe (MMSE ≤ 10), n (%)	234 (12.2)
Mean baseline NOSGER scores ± SD	
(n = 1,956)	
Memory	15.3 ± 4.1
Instrumental ADL	16.5 ± 4.9
Basic ADL	9.7 ± 4.1
Mood	12.8 ± 3.8
Social behaviour (n = 1,957)	16.0 ± 4.8
Disturbing behaviour (n = 1,957)	10.0 ± 3.6

Treatment

The mean (± SD) observation period was 3.3 ± 1.1 months of donepezil treatment. Almost half of the patients for whom complete dosage information was available (885/1,949; 45.4%) had their dose changed during this period, and in the great majority of cases this con-

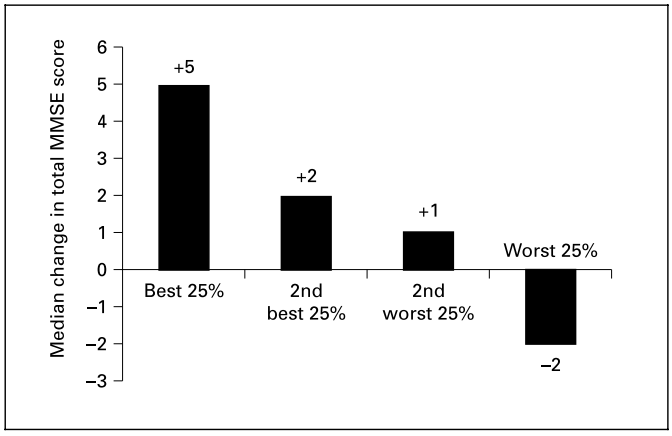

Fig. 1. Quartile analysis of change from baseline in total Mini-Mental State Examination (MMSE) score (n = 415 for all).

sisted of a single increase in donepezil dosage from 5 to 10 mg. Treatment with donepezil was stopped before the end of the planned observation period for 231 patients (11.0% of the total population). The most common reasons for discontinuation were AEs (n = 128; 6.1% of population, 55.4% of discontinuations) and treatment failure (n = 37; 1.8%, 16.0%). After the study was concluded, 77.1% of patients were to continue to receive treatment with donepezil.

Efficacy

MMSE – Cognition. There were a total of 1,660 patients with recorded MMSE scores at both study baseline and after approximately 3 months of donepezil treatment. The mean ± SD total MMSE score improved by +1.4 ± 3.6 points from baseline during the observation period (p = 0.001); the median MMSE total score improved by 1 point. Both mean and median changes in MMSE total score were comparable in patients who remained on donepezil 5 mg once daily throughout the study and in those whose doses were increased to 10 mg once daily.

A total of 63% of patients showed an improved MMSE total score (≥1 point) compared with baseline, 36.1% of patients improved by ≥3 points and 9.9% improved by ≥6 points. The quartile analysis of the MMSE data demonstrated that the best responding quartile exhibited a median improvement in total MMSE score from baseline of +5 points, while the worst responding quartile exhibited a median decline in score of –2 points (fig. 1).

In the subgroup analysis of MMSE total score changes in patients with mild, moderate or severe baseline AD symptoms (categorised according to baseline MMSE total score), mean improvements in MMSE total score from baseline were found to be greater in patients with more severe baseline disease: mean ± SD changes from baseline were +0.8 ± 3.4, +1.9 ± 3.6, and +2.3 ± 3.7 in patients with total scores of 19–30, 11–18, and 0–10 at baseline, respectively. The changes in MMSE total scores were reflected in a comparison of the proportions of patients in each dementia severity category at the end of the observation period, relative to their initial baseline category (table 2).

NOSGER. A total of 1,687 patients had NOSGER assessments both at baseline and at the end of the observation period (n = 1,688 for IADL and basic ADL dimensions). Statistically significant ($p < 0.001$) improvements (decreases) in all NOSGER dimension scores were seen in this group during donepezil treatment (fig. 2). Similarly, improvements from baseline were seen across all six NOSGER dimensions in each disease severity group, and the magnitude of the improvements was generally greater in patients with moderate or severe dementia than in those with mild disease (fig. 3).

A separate analysis of caregiver-assessed changes in seven specific AD symptoms (individual NOSGER

Table 2. Changes in MMSE category compared to baseline

	Number (%) patients in each MMSE category at the end of the observation period		
	mild	moderate	severe
Baseline MMSE category			
Mild (n = 830)	746 (89.9)	73 (8.8)	11 (1.3)
Moderate (n = 640)	226 (35.3)	368 (57.5)	46 (7.2)
Severe (n = 190)	7 (3.7)	77 (40.5)	106 (55.8)

Mild: MMSE = 19–30; moderate: MMSE = 11–18; severe: MMSE = 0–10.

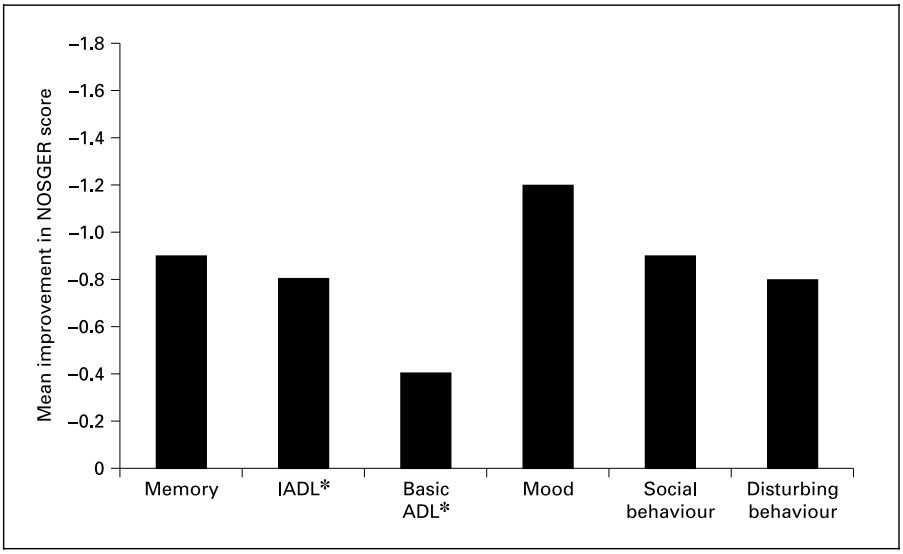

Fig. 2. Improvement in Nurses' Observation Scale for Geriatric Patients (NOSGER) dimension scores from baseline to the end of the observation period (n = 1,687; * n = 1,688).

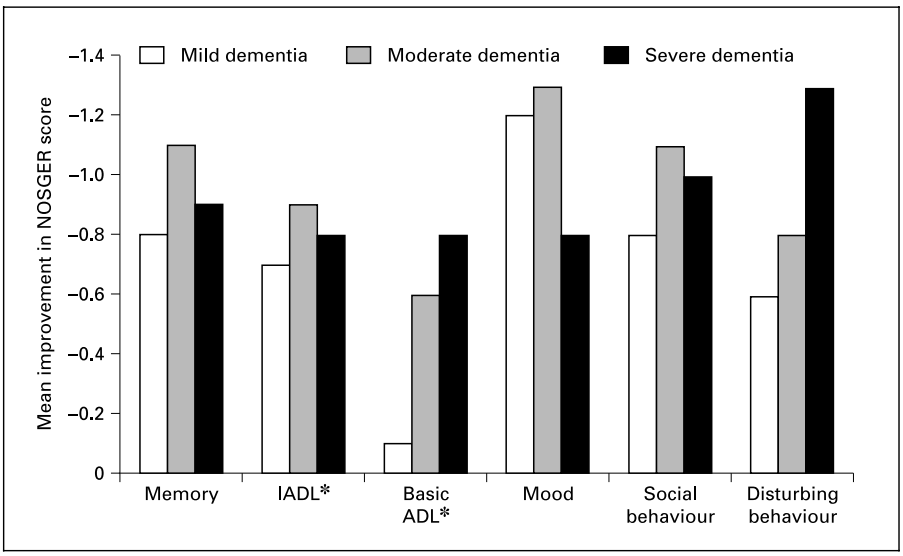

Fig. 3. Improvement in Nurses' Observation Scale for Geriatric Patients (NOSGER) scores from baseline to the end of the observation period in subgroups of patients with mild (n = 790), moderate (n = 608) and severe (n = 190; * n = 191) baseline AD symptoms (as measured by total Mini-Mental State Examination [MMSE] score).

Table 3. Number of patients with pre-existing behavioural problems and/or basic ADL deficiencies with improvements, worsening or no change in those symptoms (according to the NOSGER)

Individual NOSGER item (baseline/after treatment)*	Number (%) of patients		
	improved	worsened	no change
Night-time restlessness (n = 1,267/1,661)	545 (43.0)	108 (8.5)	614 (48.5)
Stubbornness (n = 1,268/1,675)	429 (33.8)	131 (10.3)	708 (55.8)
Irritability (n = 1,136/1,674)	401 (35.3)	105 (9.2)	630 (55.5)
Aggressive behaviour (n = 844/1676)	337 (39.9)	69 (8.2)	438 (51.9)
Urinary incontinence (n = 720/1,669)	233 (32.4)	74 (10.3)	413 (57.4)
Wandering (n = 583/1,667)	266 (45.6)	48 (8.2)	269 (46.1)
Bowel control problems (n = 565/1677)	204 (36.1)	56 (9.9)	305 (54.0)

* Based on 'observed cases' population, i.e. first number = patients with observed deficiency at baseline; second number = all patients with two evaluations (baseline and after therapy) of each NOSGER item.

Table 4. Change in investigator-rated AD symptoms in the total study population, the severe cohort*, and the ADPS cohort

Change in investigator-rated AD symptoms	Total study population (n = 1,989)	Severe population (n = 222)	ADPS population (n = 70)
Markedly improved	226 (11.4%)	29 (13.1%)	12 (17.1%)
Improved	887 (44.6%)	96 (43.2%)	35 (50.0%)
Unchanged	640 (32.2%)	66 (29.7%)	14 (20.0%)
Worsened	139 (7.0%)	20 (9.0%)	6 (8.6%)
Markedly worsened	51 (2.6%)	6 (2.7%)	3 (4.3%)
Not evaluable	46 (2.3%)	5 (2.3%)	–

* MMSE = 0–10.
ADPS = Alzheimer's disease and Parkinsonian symptoms.

Table 5. Investigator-rated tolerability of donepezil treatment for the total study population, the severe cohort*, and the ADPS cohort

Investigator-rated tolerability of donepezil treatment	Total study population (n = 1,989)	Severe population (n = 223)	ADPS population (n = 72)
Very good	1,061 (53.3%)	126 (56.5%)	41 (56.9%)
Good	754 (37.9%)	75 (33.6%)	25 (34.7%)
Moderate	76 (3.8%)	11 (4.9%)	1 (1.4%)
Unsatisfactory	98 (4.9%)	11 (4.9%)	5 (6.9%)

* MMSE = 0–10.
ADPS = Alzheimer's disease and Parkinsonian symptoms.

Table 6. Number (%) of patients reporting AEs during the observation period (only events with an incidence of ≥0.5% are listed)

AE	Patients (%) (n = 2,094)
Any AE	256 (12.2)
Nausea	46 (2.2)
Diarrhoea	30 (1.4)
Trembling inside	30 (1.4)
Vomiting	24 (1.1)
Dizziness	15 (0.7)
Restlessness	13 (0.6)
Tiredness	12 (0.6)
Confusion	10 (0.5)

items) was also performed, for those patients having behavioural problems and/or basic ADL deficiencies at baseline. There were consistently more patients showing improvements in these NOSGER items than patients showing deterioration (table 3).

Global Assessments of Change. Data from investigators' global assessments of changes in AD symptoms from baseline to the end of the observation period were available for 1,989 patients. More than half of these patients showed some degree of improvement (table 4). Global assessments of changes in symptoms were similar in patients with severe AD (table 4).

Tolerability

Global Assessments of Tolerability. Global tolerability of donepezil during the observation period was judged by the investigators to be 'very good' or 'good' in 1,815 (91.3%) of a total of 1,989 assessed patients (table 5). In the subgroup with severe AD, the global tolerability was 'very good' or 'good' in 90.1% of patients (table 5).

Adverse Events (AEs). At least one AE was reported in 256/2,094 (12.2%) patients in the total patient population and in 29/234 (12.4%) patients with severe AD. Overall, the most commonly reported AEs were psychiatric (4.4%), gastrointestinal (4.1%) and neurological (2.7%). Individual AEs with incidence greater than 0.5% are listed in table 6. The proportion of patients remaining on once-daily donepezil 5 mg throughout the observation period who experienced AEs (103/1,064; 9.7%) was similar to that of patients who had one dose increase to 10 mg once daily (52/740; 7.0%). The AE rate amongst patients who received other dose regimes (e.g. more than one dose alteration; n = 290) during the observation period was higher (101/290; 34.8%), although the most common events were still gastrointestinal, neurological or psychiatric in nature. Dose reductions in patients experiencing AEs may explain these findings.

A further subgroup analysis of the relative risks of cardiovascular AEs, including bradycardia, did not reveal any increase in rate of these AEs associated with donepezil treatment, in patients either with or without a history of cardiovascular conditions or previous treatment with beta blockers. The proportion of patients experiencing cardiovascular AEs was similar in the subgroup of patients with a history of cardiovascular conditions (11/656; 1.7%) compared with patients who had no history of cardiovascular conditions (18/1,438; 1.3%). Low and almost equal proportions of patients experienced bradycardia: 5/656 (0.8%) patients who had a history of cardiovascular conditions, and 13/1,438 (0.9%) patients without a histo-

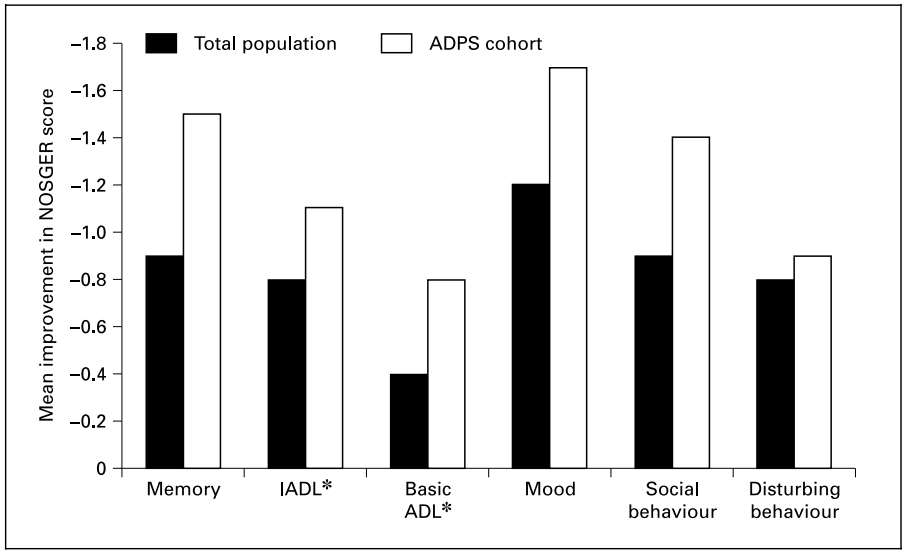

Fig. 4. Improvement in Nurses' Observation Scale for Geriatric Patients (NOSGER) scores from baseline to the end of the observation period in study cohort with AD and concomitant Parkinsonian symptoms (ADPS cohort; n = 61) and in total study population (n = 1,687; * n = 1,688).

ry of cardiovascular conditions. Similar relative risk analyses (for any AEs) in patients who had or had not taken concomitant beta blockers with donepezil showed comparable proportions of AEs. However, patients taking concomitant SSRIs showed a moderate increase in the risk of experiencing any AE during donepezil treatment. A total of 244 patients (12.0%) who did not take concomitant SSRIs (n = 2,036) experienced an AE, while 12 (20.7%) of those taking SSRIs (n = 58) did experience AEs.

Serious Adverse Events (SAEs). SAEs were reported in 46/2,094 patients (2.2%), including 6/234 patients with severe AD (2.6%). Twenty-six (56.5%) of these SAEs were considered not related to donepezil treatment. A possible or probable relation to donepezil treatment was judged to be present in 10 patients, and relation to treatment was not evaluated/evaluable for 10 patients. Four patients experienced SAEs that were considered likely or definitely related to donepezil (one each of transient nausea, vomiting, pronounced behavioural disturbance and acute urinary retention/sinus bradycardia). Fifteen deaths (0.7% of 2,094 patients) occurred, mostly from cardiovascular disease and pneumonia, but none of these were considered to be related to donepezil treatment.

Subpopulation with AD and Concomitant Parkinsonian Symptoms (ADPS Cohort)

In a post-hoc analysis, a subgroup of 73 patients was identified with documented co-morbidity of Parkinsonian symptoms (Morbus Parkinson/Parkinson syndrome/parkinsonism). The validity of this cohort was confirmed by a high prevalence of anti-parkinsonian co-medication in these patients. The baseline dementia severity (mean MMSE at study entry: 17.8 ± 5.6) in the subgroup was identical to that in the overall study population. The mean improvement in the MMSE score in the ADPS cohort was +1.7 ± 3.4 (overall study population: +1.4 ± 3.6). Figure 4 shows an analysis of NOSGER scores for the ADPS cohort, indicating larger caregiver-reported benefits across all six dimensions in the ADPS cohort compared to the overall study population. In the global clinical judgement of change in AD symptoms, donepezil treatment was considered at least as effective in the ADPS population as in the overall population (table 4).

AEs were reported in 8/73 patients in the ADPS subpopulation (11.0%), an incidence consistent with the rate of occurrence of AEs in the overall population (12.2%). Among the eight AEs in ADPS patients, no pattern of motor symptom worsening could be detected. Two SAEs were reported for the ADPS population (one death resulting from cardiac failure, one hospitalisation due to increasing disorientation), neither of which was considered related to donepezil. In the global clinical judgement of tolerability rated by the investigators, donepezil treatment showed the same excellent tolerability profile as in the overall population (table 5).

Discussion

The patients observed in this PMS study were typical of those seen in routine medical practice who are diagnosed with AD. Approximately 60% were women, which is consistent with the known sex distribution of patients with AD [33]. Furthermore, the mean age of the patients (73 years) was similar to the controlled clinical trials with donepezil and comparable to the average lifespan in Western populations [34], confirming that the population was advanced in age. Moreover, the co-morbid conditions reported were also typical of this population of elderly patients with AD.

Over 60% of the patients in the present study showed improvement on the MMSE. The mean improvement in total MMSE score of 1.4 points during the observation period was comparable to the improvement observed during 3–6 months of donepezil treatment in randomised, placebo-controlled clinical trials [21–23]. Thus, the results of this 'real world' post-marketing surveillance study of the cognitive benefits of donepezil are remarkably consistent with results demonstrated in previous controlled clinical trials.

This PMS study also demonstrates that the cognitive effects of donepezil can be substantial in patients who are particularly responsive to the agent; a median 5-point improvement in total MMSE score was observed for the top 25% of responders. It is also interesting to note that a subanalysis of cognitive response by baseline disease severity indicated that the more severe the disease, the greater the cognitive improvement. This suggests that the benefits of donepezil in clinical practice may not be limited to patients with mild to moderate disease, as were investigated in the initial clinical development programme [21–24]. Indeed, 44% of patients who initially had severe dementia in this study improved enough to be classified as having mild or moderate dementia by the end of the investigation.

In addition to the cognitive benefits demonstrated in the PMS study, the results of the NOSGER assessment are consistent with results of two different 1-year, randomised, placebo-controlled clinical trials demonstrating the beneficial effects of donepezil on daily functioning and behaviour [25, 26]. In addition, as with the MMSE results, this study provides evidence that the beneficial effect of donepezil on functional ability was more marked in patients with moderate or severe baseline disease. The observation that the effect of donepezil on the basic ADL dimension of the NOSGER was greatest in those patients with moderate or severe disease at baseline was not unexpected. Deterioration in basic ADLs normally occurs only after AD has progressed to a more advanced stage [35]. Surprisingly, however, the largest numerical improvement (in the total study population) was seen in the 'mood' domain of the NOSGER. This corroborates anecdotal experience of antidepressive effects of donepezil.

A number of individual NOSGER items reflected improvement in specific behavioural domains. Benefits of treatment with donepezil on behaviour have been reported previously [36–39], and increased attention is being given to this aspect of ChE inhibitor therapy. Behavioural symptoms are typically more prevalent as the disease progresses to the moderate and severe stages, and this is reflected in the greater improvements seen in this study in patients with moderate or severe disease at baseline.

Despite the majority of patients having co-morbid illnesses and taking concomitant medications, the overall incidence of AEs reported during the observation period was notably low at 12% of patients. Amongst the AEs reported, nausea, vomiting and diarrhoea are typical cholinergic effects of cholinesterase inhibitors, as observed in previous placebo-controlled studies [21–24]. Interestingly, the incidences of the AEs recorded in this PMS study were considerably lower (all approximately 1–2% of patients) than in the controlled trials (7% for nausea, 4% for vomiting and 9% for diarrhoea at the 5-mg dose, and higher rates for the 10-mg dose [40]). This may be explained by the naturalistic character of a PMS study, where the treating physician is likely not to ask for adverse events as specifically as in a controlled clinical trial. It was also evident that most patients whose donepezil dose was increased to 10 mg were able to tolerate the treatment as well as those who continued on the 5-mg dose. The incidence of AEs and SAEs was similar among patients with severe AD compared with the overall population, and the profile of AEs (i.e. symptoms, body systems) was similar in the total population and in patients with severe AD.

However, there was a relatively higher incidence of AEs recorded amongst patients who had more than one dose adjustment during the study. This is consistent with findings showing a relative lack of tolerance to cholinergic adverse effects amongst some patients after increases in donepezil dosage that necessitates a subsequent dose reduction. Regardless of the influence of donepezil dose changes on the incidence of AEs (or vice versa), this PMS study demonstrates that donepezil was particularly well tolerated, as shown by the investigators rating tolerability as 'good' or 'very good' in 91% of patients.

In this large observational 'study of use', donepezil treatment in those patients with AD and co-morbid Parkinsonian symptoms was at least as effective and equally well tolerated as in the overall AD study population. This ADPS cohort was of special interest because it was considered to be at high risk for the development of worsening motor symptoms after treatment with a cholinergic drug such as donepezil.

In conclusion, the combined results from two observational studies of the use of donepezil to treat AD patients in a 'real world' environment confirm the cognitive and functional benefits of the agent demonstrated in randomised controlled trials. They also indicate that donepezil is well tolerated in clinical practice. In addition to the established benefits of donepezil in patients with mild to moderately severe AD, there is evidence from this study that donepezil is effective in patients with Parkinsonian symptoms and with more severe disease. Results in patients with more severe AD confirm those reported for a recent placebo-controlled clinical trial demonstrating the efficacy of donepezil in AD patients with moderate to severe disease [37]. These efficacy and tolerability results, taken together with its once-daily dosing regimen and pharmacokinetic profile, which is not affected by dose, age, or hepatic or renal impairment, demonstrate that donepezil is an effective therapy in a broad range of patients with AD in routine clinical practice.

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