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Donepezil for Alzheimer's Disease in Clinical Practice – The DONALD Study

A Multicenter 24-Week Clinical Trial in Germany

L. Froelich[a] H.-J. Gertz[b] R. Heun[c] I. Heuser[d] K. Jendroska[e] J. Kornhuber[f] A. Kurz[g] T. Mueller-Thomsen[h] F. Ries[i] C. Waechtler[j] M. Metz[k] C. Goebel[l]

[a]Division of Geriatric Psychiatry, Central Institute for Mental Health Mannheim, University of Heidelberg, [b]Department of Psychiatry and Psychotherapy, University of Leipzig, [c]Department of Psychiatry and Psychotherapy, University of Bonn, [d]Department of Psychiatry and Psychotherapy, Charité, Humboldt University of Berlin, [e]Department of Psychiatry and Psychotherapy, Humboldt University of Berlin, [f]Department of Psychiatry and Psychotherapy, University of Erlangen, [g]Department of Psychiatry and Psychotherapy, Technical University of Munich, [h]Department of Psychiatry and Psychotherapy, University of Hamburg, [i]Practice for Neurology and Psychiatry, Bonn, [j]Klinikum Nord, Abteilung für Psychiatrie und Psychotherapie, Gerontopsychiatrie, Hamburg-Ochsenzoll, [k]Eisai GmbH, Frankfurt/Main, [l]Pfizer GmbH, Karlsruhe, Germany

Key Words

Alzheimer's disease · Dementia · Acetylcholinesterase inhibitor · Donepezil · Fischer Somatic or Undesired Effects Check List · Nurses Observation Scale for Geriatric Patients · Electrocardiography

Abstract

This multicenter open-label clinical trial was designed to investigate the safety and efficacy of donepezil, a selective acetylcholinesterase inhibitor, in the treatment of Alzheimer's disease (AD) in routine clinical practice in Germany. A total of 237 patients with mild-to-moderate AD were treated with donepezil for 24 weeks, 186 completed the study according to the protocol. In the completer group, mean MMSE score for efficacy showed an improvement from baseline of +1.6 points at week 12 (95% CI +1.1 to +2.1) and of +1.1 points at week 24 (95% CI +0.5 to +1.7). In more than 80% of the patients, global tolerability was rated to be very good or good. There were only insignificant effects on ECG parameters. This study confirms the results obtained in previous double-blind trials, which showed that donepezil is effective and well tolerated in patients with mild-to-moderately severe AD.

Introduction

Alzheimer's disease (AD) is the most common cause of dementia in the elderly. Clinically, AD is characterized by an insidious onset and a decline of memory and other cognitive functions accompanied by a gradual loss of activities of daily living. Part of the symptoms of AD can be explained by a cholinergic deficit in the cerebral cortex and other areas of the brain [1, 2]. Donepezil hydrochloride, a piperidine-based, specific and reversible inhibitor of the centrally active acetylcholinesterase (AChE) was the first second-generation AChE inhibitor to receive approval.

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Prof. Dr. Lutz Froelich
Division of Geriatric Psychiatry, Central Institute for Mental Health Mannheim
University of Heidelberg, J 5
DE–68072 Mannheim (Germany)
Tel. +49 621 1703 672, Fax +49 621 1703 673, E-Mail froelich@zi-mannheim.de

Donepezil is used for the treatment of mild-to-moderately severe AD. It results in a clinically relevant, however temporary stabilization of cognitive abilities and everyday functions and is generally well tolerated by patients with AD as demonstrated in various double-blind, placebo-controlled clinical trials [3–6]. In controlled clinical trials, patients are highly selected to fulfill regulatory requirements or to comply with safety precautions. It is uncertain, therefore, whether similar treatment results can be obtained in clinical routine, particularly when the drug is used in patients with concomitant diseases, in combination with multiple other drugs, and when the dosage is adjusted to individual needs [7]. The objective of the present open-label multi-center DONALD study (DONepezil in ALzheimer's Disease) was to investigate the safety and efficacy of donepezil in the treatment of patients with mild-to-moderately severe Alzheimer's disease in a routine setting in clinical practice.

A major focus of the study was on safety: information on adverse events (AE) was collected both from spontaneous reports by the patient and additionally by using a structured interview (FSUCL, see below) before and after the initiation of study medication. Electrocardiograms and adverse events with regard to the cardiovascular system were analyzed in detail.

Materials and Methods

The study was conducted at 37 German clinical centers (neurologic or psychiatric out-patient services and memory clinics). It was approved by independent Institutional Review Boards and was carried out in accordance with the Declaration of Helsinki and with Good Clinical Practice guidelines. Patients were required to meet ICD-10 criteria for dementia of mild to moderate severity, as defined by a Mini Mental State Examination (MMSE) score ≥ 10, and NINCDS-ADRDA criteria for probable or possible AD. Patients were allowed to have concurrent general medical and mental disorders if they received adequate treatment and were clinically stable. Main exclusion criteria were: patients without a reliable caregiver, concomitant diseases contraindicating an AchE inhibitor, sick sinus syndrome and other forms of supraventricular bradycardia, uncontrolled hypertension, history of seizures, alcohol or drug abuse. This trial was a prospective, open label, multicenter, 24-week, flexible-dose study. All patients received donepezil once daily, administered orally in the evening. Treatment was started on 5 mg/day for 28 days. Thereafter, a dose increase to 10 mg/day was allowed according to the investigator's clinical judgement. If 10 mg was poorly tolerated the dose could be reduced to 5 mg again. The patients were evaluated for safety and efficacy at baseline and after 4, 12, and 24 weeks of treatment.

Efficacy Assessment

The Mini-Mental State Examination (MMSE) [8] was used for the evaluation of cognitive function. The Clinical Global Impression of Change (CGI-C) was used for a global rating of treatment efficacy. The Nurses Observation Scale for Geriatric Patients (NOSGER) [9, 10] was used to assess six domains: memory, instrumental and basic activities of daily living, mood, social behavior and disruptive behaviors. Within each domain 5 items are rated from 1 to 5 by the caregiver. The total score of the NOSGER is 150; higher score indicate greater impairment. The NOSGER was rated by the caregiver, all other scales were scored by the study physician.

Safety Assessment

The occurrence of adverse events was obtained from patients' or caregivers' spontaneous reports. In addition, the Fischer Somatic or Undesired Effects Check List (FSUCL) [11] was used as a standardized tool for the assessment of adverse drug effects. Symptoms were rated by the study physician at baseline and after 4, 12 and 24 weeks of treatment. A FSUCL symptom was recorded as an adverse event if it was not present at baseline or if the intensity of a symptom had increased relative to the previous visit. At the end of the study the overall tolerability of donepezil was rated by the investigator on a 5-item scale (very good, good, moderate, poor or not evaluable). A standard hematological and clinical chemistry laboratory testing in a central laboratory and a complete standardized 12-lead ECG was performed at baseline and at week 24.

Statistical Analysis

There were three analysis populations. The safety population (n = 237) consisted of all patients treated with donepezil with at least one safety assessment after baseline (in 4 patients a first efficacy assessment after baseline was not done). The intention-to-treat (ITT) population (n = 233) consisted of all patients of the safety group who had at least one efficacy assessment (MMSE) after baseline. The completer population (n = 186) consisted of all patients of the ITT group who completed the 24-week study according to protocol (fig. 1). The main analysis population for the efficacy parameters was the completer population. Multiple imputation methods were used for the replacement of missing values in the ITT population [12, 13]. The FSUCL was analyzed in the ITT population. For each efficacy parameter the 95% confidence interval of the change from baseline was calculated. Pearson-Clopper 95% confidence intervals were calculated for the frequency of adverse events. Changes from baseline of the ECG parameters were investigated with Student's paired t test. Patients with cardiovascular diseases were compared to patients without cardiovascular diseases with respect to the frequency of adverse events using a logistic regression model. The adjusted odds ratios for the risk of adverse events were calculated. The model was adjusted for age ($\leq 65, >65$), sex and concurrent cardiovascular illness (yes/no).

Results

Of the 237 patients enrolled, 186 (79%) completed the study according to protocol (fig. 1). The average treatment duration was 169 days. Fifty-one (21%) patients discontinued prematurely. The reasons for drop-out were: adverse events in 29 (related to study drug in 13, unrelated to study drug in 16), withdrawal of consent in 12, lack of efficacy in 1, death in 1, and other in 8 patients. The study population was comparable to patient samples of donepe-

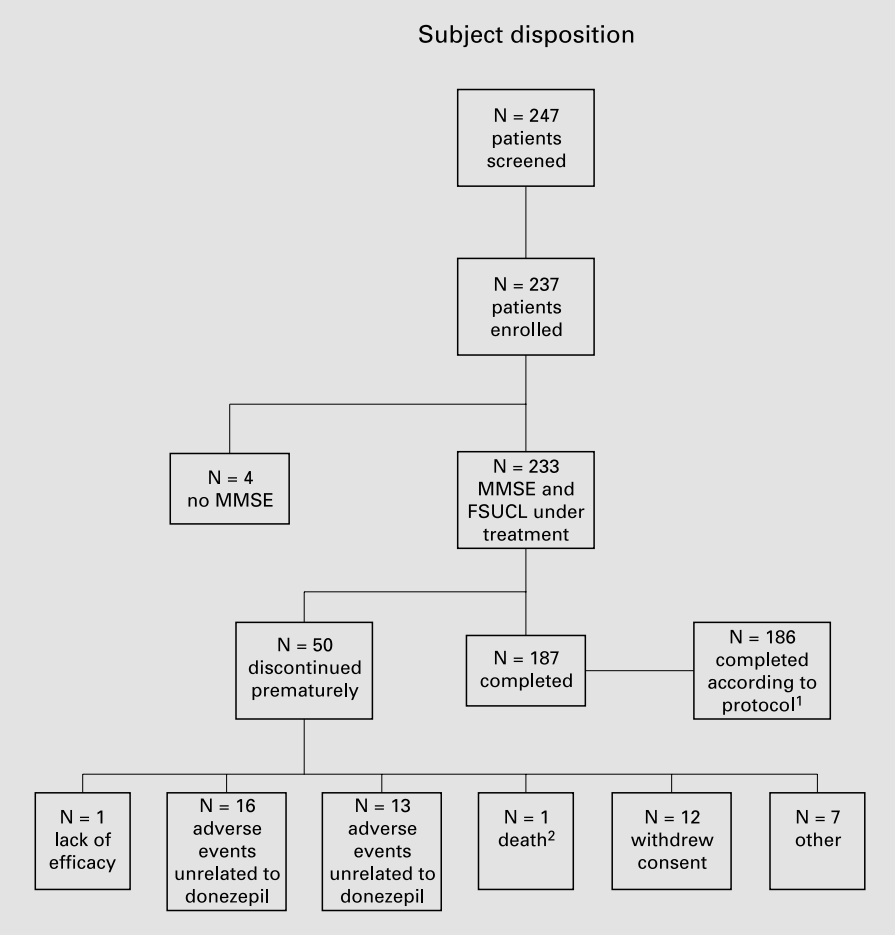

Fig. 1. Subject disposition through study. [1] One patient missed the final MMSE score and was excluded from the completer according to protocol group. [2] Cardiogenic shock not related to donepezil.

zil trials in Alzheimer's disease with regard to age and baseline MMSE scores (table 1). Approximately 90% of the patients had at least one concomitant physical illness and 86% were receiving treatment with at least one concomitant medication at baseline (table 1). 56 patients (31%) completed the study on 5 mg donepezil, 130 (69%) on 10 mg. 6 patients (3%) had their dose reduced again from 10 to 5 mg during the study.

Efficacy

The cognitive outcome of the completer group (n = 186) on the MMSE is shown in figure 2. The patients showed improvements at all visits with a peak at week 12 (+1.6 points). The change from baseline of the MMSE score was significant at all visits. The analyses of the ITT population (n = 233) revealed slightly smaller improvements, but the mean MMSE change from baseline to endpoint (+0.8 points) was still significant. At week 24, 68% of the patients had improved or remained stable relative to baseline ($\geq$3 points: 35%; $\geq$6 points: 10%). To examine the association between improvement or worsening of MMSE scores and the severity of dementia at baseline, the MMSE at baseline was analyzed in subgroups of the completer population defined by the quartiles of the MMSE change. Those patients who showed the best treatment response had the lowest MMSE scores at baseline.

With regard to the Clinical Global Impression of Change (CGI-C), 80% of the patients showed an improvement or remained stable (54% little or much improvement, 25% stable, 21% minimally or much worse) at week 24 relative to baseline (fig. 3).

With regard to the NOSGER, mean values were calculated for the maximal individual improvement in each dimension regardless of the study visit, when it occurred: These were: –1.8 points for memory, –1.6 points for social behaviour and mood, –1.3 points for disruptive behaviors, –1.2 points for IADL and –0.8 points for basic ADL. An analysis of the NOSGER dimensions in a subgroup of

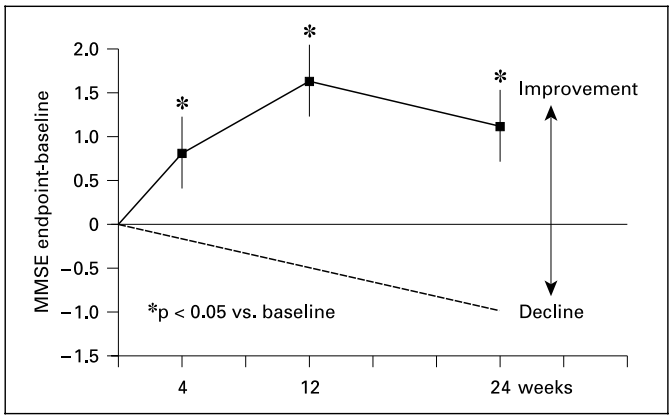

Fig. 2. MMSE difference versus baseline ± SD in patients treated with 5–10 mg donepezil for 24 weeks (■——■ ± 95% CI) compared with the course of patients treated with placebo in a 24 week double-blind trial [5] (– – –); completer group (n = 186).

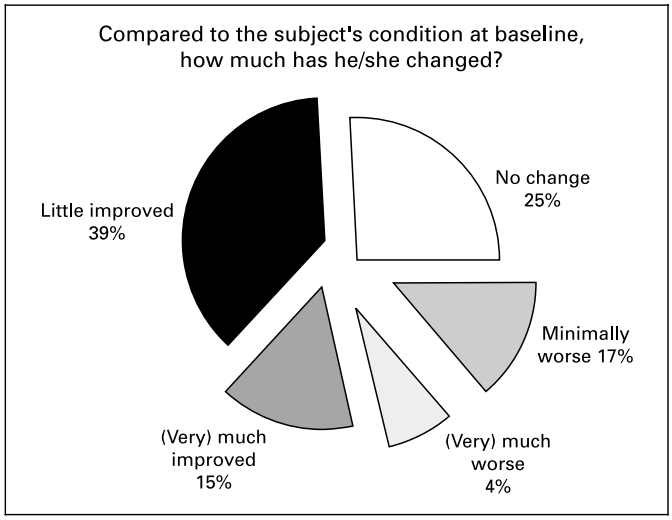

Fig. 3. Clinical global impression of change at week 24, completer group (n = 186). The study investigator was asked to answer: 'Compared to the subject's condition at baseline, how much has he/she changed?'

Table 1. Patient characteristics at baseline (n = 237)

Mean age, years ± SD (range)	70.7 ± 9.7 (46–90)
Mean weight, kg ± SD (range)	68.7 ± 11.9 (47–104)
Female patients	127 (54%)
Race, Caucasian	237 (100%)
Duration of Alzheimer's disease in months mean ± SD (median)	15.8 ± 16.6 (12)
Patient's place of living	
At home	212 (89%)
Nursing home	21 (9%)
Other	4 (2%)
Caregiver in charge of the patient	
Spouse	135 (57%)
Daughter	38 (16%)
Son	26 (11%)
Nurse	21 (9%)
Sister/brother	6 (2.5%)
Friends/neighbors	6 (2.5%)
Other	4 (2%)
Mean baseline MMSE score ± SD	19.7 ± 5.0
Patients with concomitant disease	214 (90%)
Cardiovascular	126 (53%)
Mental	64 (27%)
Endocrine/metabolic	64 (27%)
Musculosceletal disorders	54 (23%)
Patients with concomitant drugs	203 (86%)
Cardiovascular	134 (57%)
Central nervous system active drugs	95 (40%)
Drugs for musculosceletal disorders	84 (35%)

patients, who already had a marked impairment at baseline, based on defined cut-off points [10], showed improvements in all dimensions at week 24 (fig. 4).

Safety

In the safety analysis group (n = 237) there were no relevant changes in vital signs, i.e. mean blood pressure was 138/81 mm Hg at baseline and 136/79 mm Hg at week 24 and mean heart rate 74/min at baseline and 70/min at week 24.

A total of 172 subjects (73%) experienced at least one treatment emerging adverse event. Most of these events were mild to moderate and transient. A total of 29 patients (12%) who received donepezil discontinued treatment due to adverse events: cardiovascular events (5 patients, 2.1%), agitation (3 patients, 1.3%), nausea or vomiting (3 patients, 1.3%), muscle cramps (3 patients, 1.3%), urinary incontinence (3 patients, 1.3%), fecal incontinence (2 patients, 0.8%), abdominal pain (2 patients, 0.8%), diarrhea (2 patients, 0.8%), fatigue (2 patients, 0.8%), and headache (2 patients, 0.8%). Adverse events with an incidence >5% are listed in table 2.

Serious averse events (SAE) occurred in 22 subjects (9%) of the patients. The most common SAE were falls; in singular cases pain syndromes, orthostatic hypotension, pneumonia and others occurred. According to the investigators' judgment, no SAE was related to donepezil treatment.

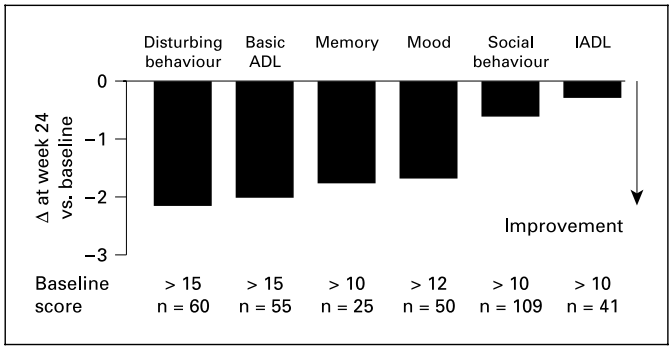

Fig. 4. Mean improvement of NOSGER domains at week 24 of patients with defined impairment at baseline for each NOSGER domain [cut-off definitions from reference 10]; completer group (n = 186).

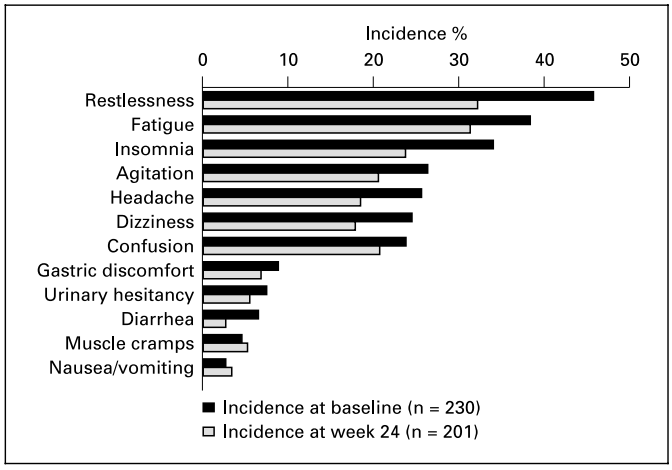

Fig. 5. Incidence of frequent (>20%) or AChEI-specific FSUCL symptoms at baseline and week 24.

The most frequent FSUCL symptoms present at baseline were symptoms commonly observed in patients with AD. The number of patients with symptoms of cholinergic overstimulation either decreased (gastric discomfort, urinary hesitancy and diarrhea) or increased only slightly (muscle cramps, nausea/vomiting) during the study (fig. 5). A discrete increase in frequency (1–2% from baseline) of FSUCL symptoms from baseline to week 24 could only be observed for six of the 26 FSUCL domains, i.e. disturbance of visual accommodation, appetite, muscle cramps, hyperkinesia, nausea/vomiting, and akathisia.

Global tolerability was rated to be very good or good in 81.1% of the patients. There were no relevant laboratory abnormalities observed at baseline or week 24.

Cardiovascular Safety

The overall incidence of cardiovascular events was low considering the advanced age and comorbidity of this patient population. Cardiovascular adverse events including falls with a frequency of ≥1% are listed in table 3. Patients with cardiovascular diseases were compared to patients without cardiovascular diseases with respect to the incidence of adverse events. Odds ratios for the risk of adverse events showed no significant differences between these two groups.

In a retrospective analysis of 12-lead ECG recordings at baseline and week 24 by an independent ECG specialist, a total of 134 patients were evaluable, having readable ECGs at both visits. The ECGs were analyzed for cholinergic effects, i.e. for an influence on heart rate and PQ

Table 2. Incidence of adverse events >5%: safety population (n = 237)

	n	%	Severity		
			mild	moderate	severe
General					
Fatigue	35	14.8	17	13	5
Psychiatric					
Agitation	58	24.5	21	25	12
Anorexia	23	9.7	15	7	1
Insomnia	31	13.1	17	10	4
Central and peripheral nervous system					
Confusion	28	11.8	12	11	5
Dizziness	21	8.9	13	7	1
Headache	32	13.5	19	12	1
Hyperkinesia	15	6.3	8	4	3
Tremor	15	6.3	10	5	0
Gastrointestinal					
Abdominal pain	19	8.0	12	7	0
Diarrhea	15	6.3	7	4	4
Nausea	23	9.7	11	8	4
Autonomic nervous system					
Mouth dry	18	7.6	14	3	1
Sweating increased	18	7.6	7	6	5
Musculoskeletal					
Muscle cramps	16	6.8	8	5	3

Table 3. Incidence of cardiovascular adverse events >1%: safety population (n = 237)

	n	%	Severity		
			mild	moderate	severe
Body as a whole					
Accidental fall	5	2.1	2	1	2
Cardiovascular					
Bradycardia	6	2.5	6	0	0
Extrasystoles	3	1.3	3	0	0
Hypertension	4	1.7	2	0	2
Postural hypotension	11	4.6	10	1	0
Syncope	4	1.7	1	2	1
Tachycardia	3	1.3	3	0	0

intervals. Mean heart rate decreased from 70 bpm (range 39–115) to 68 bpm (range 40–108). Mean PQ interval increased from 169 ms (range 110–260) to 172 ms (range 120–250). The difference between baseline and week 24 was not statistically significant for both parameters (Student's t test). In conclusion, donepezil seemed to have an insignificant cholinergic effect on heart rate (decrease by 2 bpm) and PQ interval (increase by 3 ms), which was not associated with higher incidences of cardiovascular adverse events, atrioventricular (AV) blocks or serious adverse events. In particular, from 10 patients with I° AV block (PQ interval ≥200 ms) at baseline, only two patients had a mild increase of the PQ interval at week 24, one from 210 ms to 220 ms, one from 240 ms to 250 ms. Both patients had no cardiovascular adverse event during the study. The other 8 patients with I° AV block had a decrease of the PQ interval at week 24. One of these eight patients had a cardiovascular event (postural hypotension) during the study. Four of the 237 patients had a decrease in heart rate from >50 bpm at baseline to <50 bpm at week 24. None of these patients had a cardiovascular adverse event other than bradycardia during the study.

Discussion

This current open label study recruited 237 patients with mild to moderately severe AD; in 186 patients who completed the study the MMSE scores showed a moderate increase from baseline at all visits during the study period. These changes on the MMSE are consistent with results of placebo-controlled trials [3–6]. The deterioration of MMSE scores in untreated AD patients is approximately 2.8 points per year [15, 16]. Although a fluctuation of 1–2 points on MMSE can be seen as part of the natural course of AD, a mean increase of 1.4 points thus corresponds to a delay in the decrease of cognitive function of about one year. This change in MMSE is in rough accordance with data from controlled clinical trials in AD with ADAS-cog as primary outcome measure [5, 6, 14]. These data and the fact that over 1/3 of these patients (35%) showed an improvement of ≥3 points in MMSE in our study demonstrates that the beneficial effects of donepezil on cognitive function in AD are of clinical relevance.

In the majority of patients, the NOSGER, which was rated by the caregiver, showed only mild impairments at baseline. Nevertheless, a small, but significant improvement was demonstrated at the end of the study compared to baseline in all domains for those patients who had impaired function at baseline (fig. 4). Maximum improvement was achieved in the domains consistent with memory, mood and disruptive behavior. Drug effects on functional behavior, i.e. those areas that are most problematic and stressful to caregivers, are generally more pronounced in patients with moderate-to-severe AD [9]. Although the clinical relevance of the improvements on the NOSGER is debatable, the finding that according to caregivers' reports there was no loss of function during the study period certainly is significant.

Donepezil was well tolerated in this trial. Adverse events (AE) occurred in 73% of the patients, the majority of them were rated to be mild in severity and transient. This is consistent with findings of earlier placebo-controlled studies [3–6] and observational studies from clinical practice [17, 18]. The undesired effects collected with the FSUCL generally decreased in frequency over the course of the study and thus, cannot simply be regarded as adverse events due to study medication. Additionally, the most frequent FSUCL symptoms present at baseline were symptoms common in AD and possibly attributed to the disease itself (fig. 5).

The incidence of specific adverse symptoms related to cholinergic symptoms was relatively low and either decreased (gastric discomfort, urinary hesitancy and diarrhea) or increased only slightly (muscle cramps, nausea/vomiting) during the study (fig. 5). The low incidence of cholinergic side effects might be attributed to the flexible dose regimen used in this study.

Cholinergic effects on the cardiovascular system were evaluated in detail because the prevalence of cardiovascular concomitant diseases is considerable in this age group and is of particular clinical relevance. Cardiovascular

adverse events were infrequent in this trial and there was no increased risk for patients with cardiovascular disease. The insignificant decrease in heart rate by 2 bpm in the present study is comparable to the decrease of 2– 5 bpm as observed in the US [21]. In an observational cohort study in England, 1,762 patients (mean age 72.9 years; 42% male) were followed up for 6 months minimum and no cardiac rhythm disturbances or liver disorders were found to be causally associated with donepezil [22]. However, it is of interest to note that there has been a case report on a prolongation of the QT interval in a dementia patient due to rivastigmine [23].

In conclusion, this open-label study conducted in routine clinical practice confirms and extends the results obtained from double-blind controlled clinical trials. It shows that donepezil is effective and improves cognition, preserves function and is well tolerated in patients with mild-to-moderate AD. In addition, the low frequency of the typical cholinergic adverse effects (nausea, diarrhea, muscle cramps) observed in this trial using a structured instrument, and the insignificant effects on the ECG parameters, adds additional evidence to the favorable tolerability profile of donepezil.

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