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Galantamine Provides Sustained Benefits in Patients with 'Advanced Moderate' Alzheimer's Disease for at Least 12 Months

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Advanced disease · Alzheimer's disease · Galantamine · Long term

Abstract
Galantamine (Reminyl®), a novel agent with a dual mode of action, modulates nicotinic acetylcholine receptors and inhibits acetylcholinesterase. Galantamine has consistently demonstrated a broad range of beneficial effects and has shown sustained benefits in cognitive and functional abilities for at least 12 months in patients with mild-to-moderate Alzheimer's disease (AD). As pivotal studies demonstrating the efficacy of cholinergic drugs were designed to exclude patients with severer AD, many patients with the advanced stage of this condition are currently not treated due to the lack of demonstrated efficacy in clinical trials. We aimed to investigate whether there was any evidence for the benefits of galantamine in patients with severer disease, by performing a post hoc analysis using data extracted from the population of the two long-term galantamine studies. We evaluated the efficacy of galantamine in patients with 'advanced moderate' AD. 'Advanced moderate' patients were those with baseline Mini Mental State Examination (MMSE) scores ≤ 14 or Alzheimer's Disease Assessment Scale – cognitive subscale (ADAS-cog) scores >30. These patients were compared with matched controls who received placebo in a different historical study. Cognitive abilities (assessed using the ADAS-cog scale) of 'advanced moderate' AD patients receiving galantamine for 12 months were maintained at baseline levels after 12 months, and significantly improved over those of placebo patients ($p < 0.001$). Of the 'advanced moderate' patients receiving galantamine, 51% with baseline ADAS-cog of >30 maintained or improved their ADAS-cog scores over baseline values, compared with 13% receiving placebo ($p < 0.001$). In the subgroup of 'advanced moderate' patients with baseline MMSE ≤ 14, 48% of those receiving galantamine and 4% of those receiving placebo maintained or improved their ADAS-cog scores at 12 months ($p = 0.001$). In both subgroups, the treatment difference (galantamine vs. historical placebo) amounted to approximately 10 points on the ADAS-cog scale. Functional abilities, as assessed using the Disability Assessment for Dementia scale, remained significantly superior in galantamine-treated patients compared with historical placebo-treated patients at 12 months ($p < 0.001$). In conclusion, galantamine offered sustained efficacy to patients with 'advanced moderate' AD, confirming the benefits seen in published studies of patients with mild-to-moderate AD. This drug has potential for broader use in clinical practice.

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Galantamine (Reminyl®) is a novel agent with a dual mode of action. It enhances the effects of acetylcholine by modulation of the nicotinic acetylcholine receptors and inhibits acetylcholinesterase from degrading released acetylcholine [1]. Galantamine has consistently demonstrated beneficial effects on cognitive, functional and behavioural symptoms in patients with mild-to-moderate Alzheimer's disease (AD), in randomized, prospective studies [2–7]. Beneficial effects of galantamine are sustained for at least 12 months in these patients [4].

Four phase III studies have been performed to assess the efficacy and safety of galantamine in patients with mild-to-moderate AD in Australia, Canada, Europe, South Africa and the USA [2–5]. Due to ethical considerations and widespread professional and public awareness about the effectiveness of available agents, it has not been feasible to perform placebo-controlled studies over 12 months. However, at the end of the two 6-month studies, patients who still met the inclusion criteria, including those randomized to placebo, were eligible to enter 6-month, open-label extension studies (total study duration 12 months) using galantamine 24 mg/day [4, 6]. Patients with mild-to-moderate AD – who received galantamine 24 mg/day for 12 months (i.e. in the double-blind *and* open phases) – had preserved cognitive function at or above baseline levels [4, 6]. Furthermore, patients with mild-to-moderate AD who received galantamine 24 mg/day throughout the trial had a better cognitive function at the end of the studies than those who received placebo for the first 6 months. Nevertheless, a significant improvement in cognition was seen in the latter group of patients following the initiation of galantamine treatment. These data suggested that patients who began treatment at a later stage benefited from treatment to a similar extent as those who began the treatment earlier. However, since they started from a lower baseline point (following 6 months of decline on placebo), they reached an inferior endpoint, indicating that earlier treatment with galantamine may the optimize long-term outcome.

The cholinergic deficiency hypothesis of AD attributed memory and other impairments to the putative degeneration of brain cholinergic neurons and indicated that enhancing cholinergic neurotransmission with the help of cholinergic drugs might improve symptoms. Furthermore, it was postulated that this strategy could only be effective in patients with non-advanced AD, who still maintain a certain substrate of functioning cholinergic neurons on which the cholinergic drugs could be active. As a result, clinical trial requirements imposed by regulatory authorities have not encouraged the assessment of new pharmacotherapies in all types of patients with AD. Historically, studies evaluating new treatments for this condition have therefore focused upon patients with mild-to-moderate stage AD, such as those described above in the published galantamine studies. However, relatively recent studies have indicated that cholinergic drugs might be effective in all – mild, moderate and severe – AD. Davis et al. [8] found that, although neocortical cholinergic deficits are characteristic of severely demented patients with AD, overt cholinergic deficits do not generally appear until relatively late in the course of the disease. For instance, choline acetyltransferase starts to decline at a Clinical Dementia Rating score of 2 and acetylcholinesterase activity at a score of 5. One study with a cholinesterase inhibitor has since shown some efficacy in patients with 'moderate-to-severe' AD [9].

We aimed to investigate whether there was any evidence for the sustained benefit (over 12 months) of galantamine in patients with severer disease within the galantamine efficacy database. As recognized in the AD treatment guidance from the UK National Institute for Clinical Excellence (NICE), there is wide consensus that Mini Mental State Examination (MMSE) scores ≤ 12 represent severe AD [10]. On the Alzheimer's Disease Assessment Scale – cognitive subscale (ADAS-cog), this equates approximately scores of >30 points. The consistency of long-term galantamine trial designs [7] allowed data to be pooled for patients who had baseline MMSE scores ≤ 14 or ADAS-cog scores >30 when they entered the original studies. Although these patients had, by definition for the phase III study entry criteria, mild-to-moderate AD (baseline MMSE 11–24 and ADAS-cog ≥ 12), their conditions were at the more advanced edge of these limits and were therefore described as having 'advanced moderate' AD. A post hoc analysis of the effects of galantamine in these 'advanced moderate' patients was then performed.

Conducting long-term, placebo-controlled trials involving patients with AD is not appropriate, and this presents difficulties in assessing the long-term efficacy and tolerability of antidementia drugs. However, there are various methods of comparing the long-term decline in treated versus untreated patients. One way is by simple or quadratic extrapolation of short-term placebo changes, such as the method of Stern et al. [11]. However, this results only in theoretical 'generated' data. The use of historical comparator data also has limitations, although appropriately chosen historical cohorts can be useful in quantifying long-term benefits. Recently, data from two 12-month, placebo-controlled sabeluzole studies in mild-to-moderate AD, with similar outcome measures as those

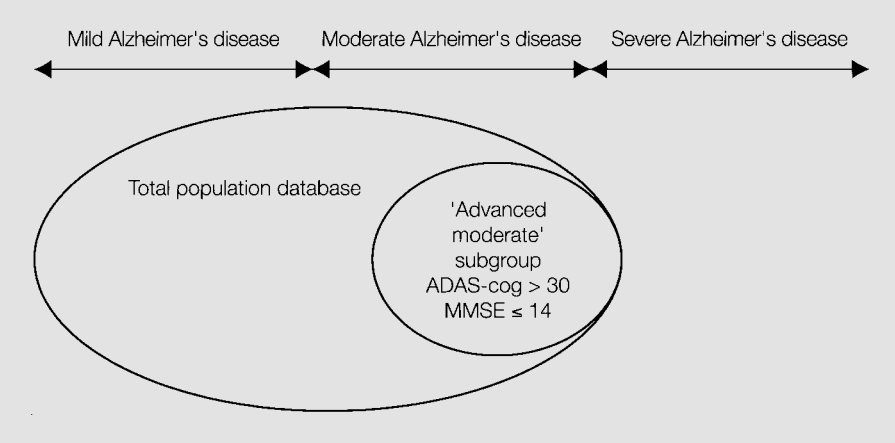

Fig. 1. The analysis of patients with 'advanced moderate' AD used two subsets of patients from the more advanced end of 'mild-to-moderate' AD – those with baseline ADAS-cog scores of >30 and those with baseline MMSE scores ≤14.

used in the open-label galantamine study, have become available. The patients in these studies had similar inclusion and exclusion criteria, baseline characteristics and demographics to those of patients in the galantamine trials [9, 12], which therefore allowed valid comparisons between galantamine-treated and control patients to be made.

We performed this study in order to answer the following questions:

Is the efficacy of galantamine sustained for at least 12 months in patients with 'advanced moderate' AD?

Are patients with 'advanced moderate' AD at a greater risk of side-effects from treatment?

Methods

Design of Phase III Studies

All phase III studies were randomized, double-blind, placebo-controlled, multicentre trials conducted in Australia, Canada, Europe, South Africa and the USA [2–5]. At the end of the 6-month studies, patients who still met the inclusion criteria were eligible to enter 6-month extension studies (total study duration 12 months) using galantamine 24 mg/day [4, 6]. Patients were re-titrated with galantamine after completion of the placebo-controlled study phase. Patients had mild-to-moderate AD, defined as baseline MMSE scores of 11–24 and a score ≥12 on the ADAS-cog. In all studies, the primary efficacy measure was change in cognition, as assessed using the ADAS-cog [13]. Functional abilities were assessed using the Disability Assessment for Dementia (DAD) scale [14] in the 3-month study [2], the two 6-month studies [4, 6] and the two open-label extensions [4, 6]. The 5-month study used the AD Cooperative Study/Activities of Daily Living inventory [15] in functional analyses. Functional AD Cooperative Study/Activities of Daily Living results from this single study were, therefore, not included into the pooled analysis, as the number of patients with 'advanced moderate' AD (as defined below) did not warrant adequate statistical appraisal [3].

Analysis of Patients with 'Advanced Moderate' AD

Two subgroups of 'advanced moderate' AD patients were defined and identified using separate data filters from the patient population of both open-label extension studies: patients with a baseline MMSE ≤14; patients with a baseline ADAS-cog score >30.

The MMSE filter was applied to the database primarily because MMSE ≤12 is recognized in clinical practice, and by regulatory bodies such as NICE, as indicating severe AD. The ADAS-cog assesses similar parameters as the MMSE, but it is more sensitive to change. The equivalent ADAS-cog filter was therefore applied in order to be able to draw firm statistical conclusions that backed up the MMSE data. Importantly, application of both MMSE and ADAS-cog filters to the same database necessarily introduced some overlap of patients' data between the MMSE and ADAS subgroups. Nevertheless, this dual analysis allowed independent and complementary statistical conclusions to be drawn for both patient data sets.

These patients are classified as having 'mild-to-moderate' AD, but they are towards the 'severe' end of that category (fig. 1); therefore, we describe them as having 'advanced moderate' AD. The benefits of galantamine in these patients were assessed by evaluating their responses on the ADAS-cog, DAD and Clinician's Interview-Based Impression of Change plus Caregiver Input scales. However, the latter data were considered unreliable after month 6, since the start of the open extension phase was used as a new reference time point by some of the investigators; therefore these data are not reported.

In addition, historical placebo data were obtained from appropriate subsets of patients (stratified according to baseline cognitive abilities: ADAS-cog >30 or MMSE ≤14) from two previous 12-month, placebo-controlled studies that evaluated sabeluzole in patients with mild-to-moderate AD. These studies incorporated similar inclusion criteria and outcome measures, and patients showed similar baseline characteristics as in long-term galantamine studies [9, 12]: <85 years of age; established diagnosis of clinically probable AD (National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria); mild-to-moderate disease severity (MMSE scores

Table 1. Baseline characteristics of patients with 'advanced moderate' AD

	Baseline ADAS-cog >30		Baseline MMSE ≤14	
	galantamine 24 mg/day	placebo	galantamine 24 mg/day	placebo
Patients	69	96	26	46
Mean age, years	73.7 ± 0.99	74 ± 0.84	72.7 ± 1.45	72.6 ± 1.31
Number receiving concomitant medications	57 (82.6)	NA	24 (92.3)	NA
Mean ADAS-cog	37.3 ± 0.71	37.4 ± 0.50	39.0 ± 1.42	34 ± 1.11
Mean MMSE	15.9 ± 0.39	16.0 ± 0.22	12.5 ± 0.24	14 ± 0.00[1]
Mean DAD	56.7 ± 2.43	51.6 ± 2.03	52.1 ± 4.30	54.2 ± 2.72

Results are expressed as means ± SE; figures in parentheses indicate percentages. NA = Data not available.

[1] Note that that standard error of mean MMSE scores in the MMSE ≤14 group was zero, as only patients with MMSE = 14 were selected from sabeluzole studies.

14–22); cognitive decline; no evidence of another cause for dementia; efficacy measured with ADAS-cog and DAD. Thus, these data allow valid comparisons of long-term outcomes between galantamine and historical placebo cohorts.

Statistical Analyses

All randomized patients who received at least one dose of trial medication were included in the analyses of baseline characteristics. For our post hoc analysis of 'advanced moderate' patients, the primary statistical analysis was performed on the intention to treat population, using observed case data, as was done in the individual trials.

Changes in ADAS-cog and DAD scores were compared between the treatment groups by means of analysis of variance. Possible effects of baseline characteristics on efficacy findings were tested using an analysis of covariance (ANCOVA). Responder rates on ADAS-cog (improved or maintained baseline scores) were also calculated and compared by means of Fisher's exact test.

Results

Demographics

In the original phase III open-label extension studies [4, 6], 257 patients with mild-to-moderate AD received galantamine 24 mg/day for 12 months. Another 291 patients received placebo for the first 6 months (double-blind phases of each study) and switched to galantamine for the latter, open-label, 6-month extension phases of each of the12-month studies. In the historical sabeluzole studies, from which data were collected to provide 12-month placebo data, 455 patients with mild-to-moderate AD received placebo for 12 months [9, 12].

Sixty-nine and 96 patients receiving galantamine 24 mg/day and historical placebo, respectively, for 12 months had baseline ADAS-cog scores >30. Sixty-six patients received placebo for the first 6 months, followed by open-label galantamine for 6 months.

Twenty-six and 46 patients receiving galantamine 24 mg/day and placebo, respectively, had baseline MMSE scores ≤14. Thirty-two patients received placebo for the first 6 months followed by open-label galantamine for 6 months.

The baseline characteristics of these two 'advanced moderate' subgroups are shown in table 1. All patients had responsible caregivers and were living in the community at the start of the study. Other than baseline AD severity, baseline characteristics were similar to those seen in the overall populations of the four phase III studies [2–5]. To establish whether the small difference between galantamine and placebo baseline cognitive scores in MMSE ≤14 patients (table 1) had any effect on the outcome results, baseline cognitive scores were included as a covariate in an ANCOVA of efficacy. All ANCOVA tests confirmed no significant effects on cognitive outcomes ($p > 0.1$).

Cognitive Abilities

By the end of the 6-month, placebo-controlled study, ADAS-cog scores were significantly improved with galantamine over placebo, in patients who had baseline ADAS-cog scores >30 when they joined the studies ($p < 0.001$; fig. 2a). The decline observed in the pooled placebo group from galantamine studies was similar at month 6 to that observed in placebo-treated patients in the historical sabeluzole study, supporting the use of these historical data (fig. 2a). At month 6, mean (±SE) ADAS-cog scores in galantamine-placebo patients declined by 4.4 ± 0.65

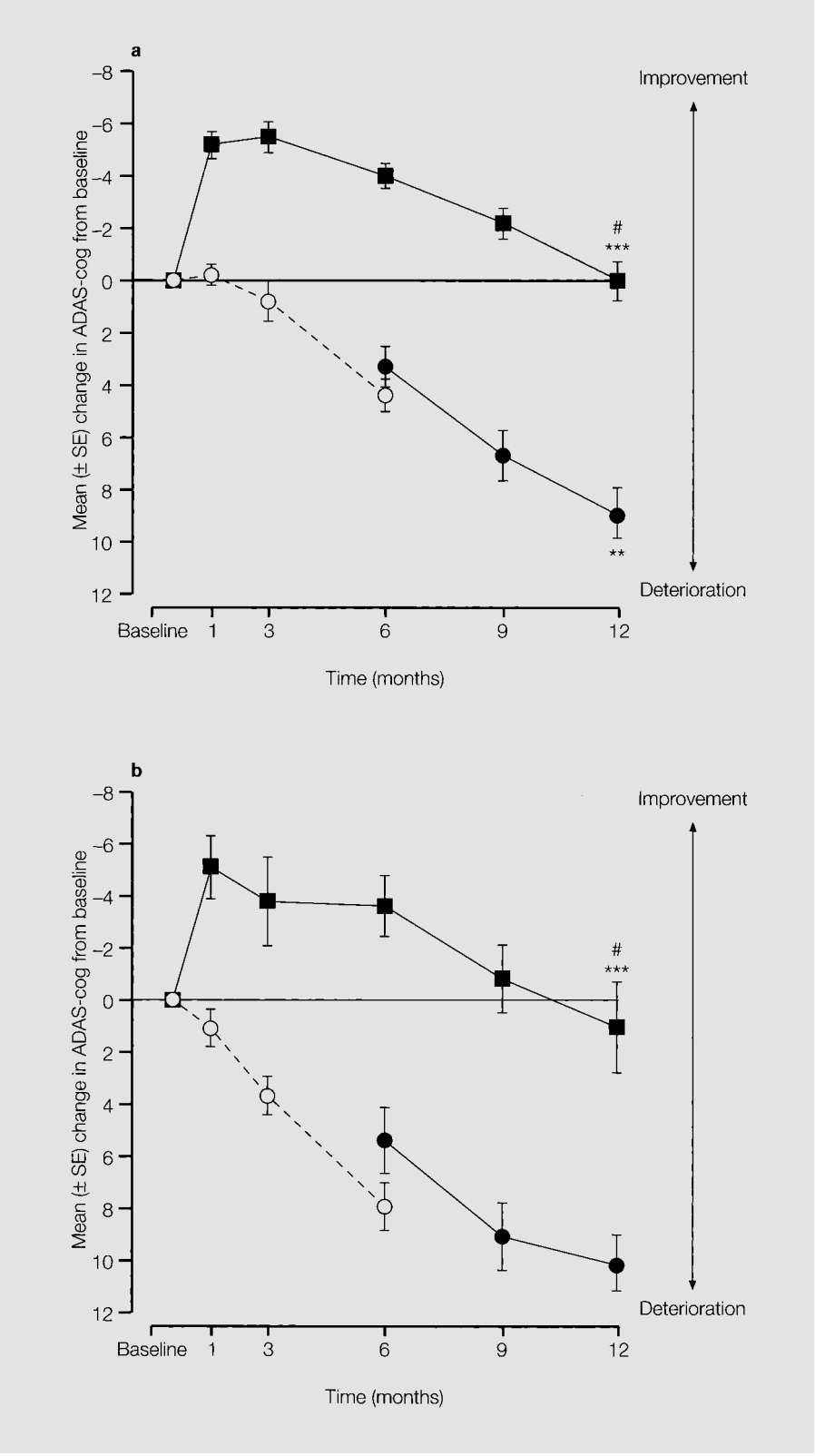

Fig. 2. Patients with 'advanced moderate' AD with baseline ADAS-cog scores >30 (a) and patients with a baseline MMSE ≤14 (b) maintained baseline cognitive abilities for at least 12 months, compared with a significant decline in the historical placebo group. ■ = Galantamine 24 mg/day (a: n = 69, b: n = 26); ○ = placebo in the double-blind phase (a: n = 66; b: n = 32); ● = historical placebo data (a: n = 96; b: n = 46); ** $p < 0.01$; *** $p < 0.001$; # not significant versus baseline.

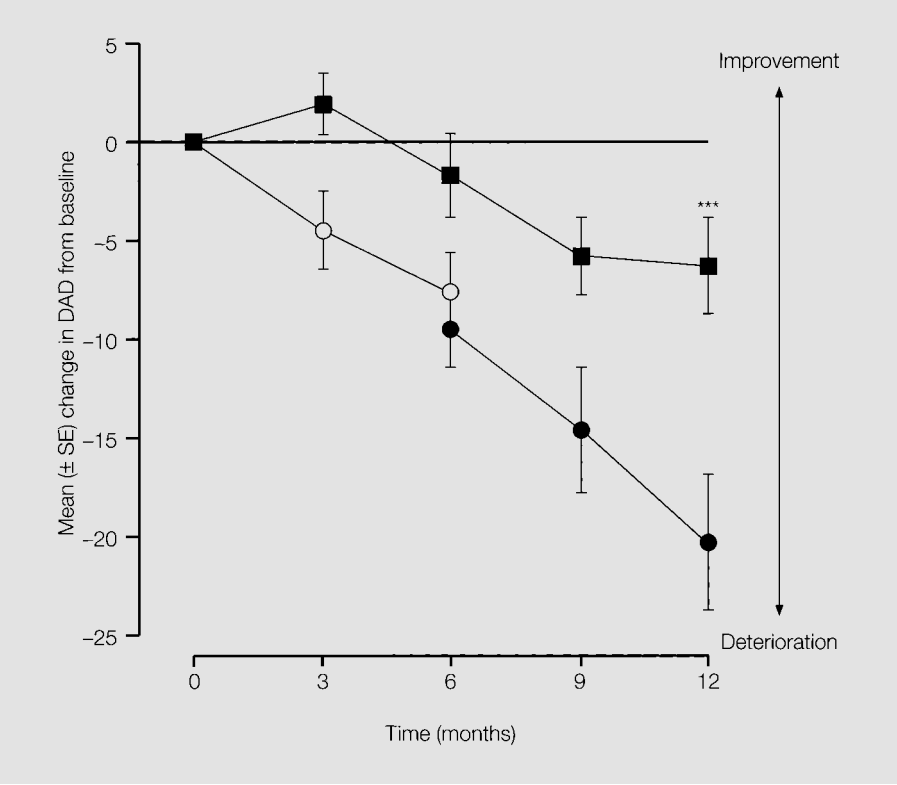

Fig. 3. Patients with 'advanced moderate' AD with baseline ADAS-cog scores >30 had significantly improved functional abilities over those patients in the historical placebo group. ■ = Galantamine 24 mg/day (n = 66); ○ = placebo in the double-blind phase (n = 65); ● = historical placebo data (n = 77); *** $p < 0.001$ versus placebo.

points in the ADAS-cog >30 group and by 8.0 ± 0.82 points in MMSE ≤14 patients. In the sabeluzole studies, mean (±SE) ADAS-cog scores deteriorated by 3.4 ± 0.80 and 5.5 ± 1.21 points in ADAS-cog >30 and MMSE ≤14 patients, respectively. A least-squares mean change comparison showed no statistically significant difference between 6-month cognitive decline in galantamine-placebo patients and sabeluzole-placebo patients ($p = 0.327$ for the ADAS-cog >30 group and $p = 0.111$ for the MMSE ≤14 group).

Patients who had received galantamine for the full 12 months maintained ADAS-cog scores at or above baseline levels at month 12, compared with a significant decline of 9.2 points in the historical placebo group (fig. 2a). The treatment difference (galantamine vs. placebo) amounted to nearly 10 points ($p < 0.001$).

Similar results were observed in patients with 'advanced moderate' AD, stratified according to their baseline MMSE scores ≤14 (fig. 2b). At 12 months, these patients who had received galantamine for the full 12 months maintained ADAS-cog scores at or above baseline levels compared with a significant decline of 10.3 points in the historical placebo group (fig. 2b).

At 12 months, 51% of patients with baseline ADAS-cog scores >30 improved or maintained these scores (improvement of ≥0 points) compared with 13% of these patients in the 12-month historical placebo group ($p < 0.001$). In the subgroup of patients with baseline MMSE ≤14, 48% of those who received galantamine for 12 months and 4% of those in the historical placebo group improved or maintained ADAS-cog scores ($p = 0.001$).

Functional Abilities

At 12 months, patients with baseline ADAS-cog scores >30 at the time of joining the studies, who had received galantamine for the full 12 months, maintained DAD scores above levels observed in the historical placebo group. Galantamine-treated patients deteriorated by 6.3 points on the DAD scale, while historical placebo patients receiving placebo for 12 months deteriorated by 20.3 points (39% of baseline score) on the DAD scale (treatment difference 14 points, $p < 0.001$; fig. 3). At 12 months, 39% of patients with baseline ADAS-cog >30 improved or maintained DAD scores (improvement of ≥0 points) compared with 12% of these patients in the historical placebo group ($p = 0.001$).

Table 2. Adverse events reported by at least 10% of patients in both subgroups of 'advanced moderate' AD patients compared with rates observed in the total database of patients with mild-to-moderate AD

Adverse events (preferred term)	'Advanced moderate' population		Total population (n = 257)
	ADAS-cog >30 (n = 69)	MMSE ≤14 (n = 26)	
Nausea	19 (27.5)	4 (15.4)	98 (38.1)
Vomiting	7 (10.1)	3 (11.5)	47 (18.3)
Dizziness	11 (15.9)	3 (11.5)	44 (17.1)
Diarrhoea	12 (17.4)	6 (23.1)	40 (15.6)
Rhinitis	7 (10.1)	4 (15.4)	28 (10.9)
Weight decrease	8 (11.6)	4 (15.4)	27 (10.5)
Confusion	7 (10.1)	4 (15.4)	21 (8.2)
Abdominal pain	9 (13.0)	3 (11.5)	20 (7.8)

Figures in parentheses indicate percentages.

Data on functional abilities, as assessed using the DAD scale for patients with baseline MMSE ≤14, produced comparable response rates; 38.1 and 17.2% of patients showed improvement or no change in mean DAD scores at month 12. Although a substantial (20.9%) advantage is seen for galantamine, this difference in treatment response did not achieve statistical significance ($p > 0.05$), probably because of low numbers of patients available for statistical analysis (n = 13 for galantamine and n = 24 for historical placebo). Mean changes in DAD scores in MMSE ≤14 patients reflected this; mean DAD scores fell from 52.1 ± 4.30 at baseline to 42.8 ± 5.48 at month 12 with galantamine 24 mg/day, and those of placebo patients fell by 14.5 points ($p > 0.05$).

Safety

Galantamine was well tolerated in patients with 'advanced moderate' AD. The majority of adverse events were mild to moderate in severity and predominantly gastro-intestinal. Table 2 lists adverse events reported in more than 10% of patients. Placebo safety data were unavailable for our analysis, therefore table 2 compares the rates of the most frequent adverse events in 'advanced moderate' AD patients with the rates of these events observed in the total database of patients with mild-to-moderate AD. Nausea was the most frequently reported adverse event associated with galantamine treatment. While the incidence of nausea was around 10–20% lower in 'advanced moderate' AD patients compared with the total mild-to-moderate AD group, the incidence of diarrhoea was slightly higher (by around 2–7%). Vomiting was reported in just 10.1% of patients with baseline ADAS-cog >30 and 11.5% of those with baseline MMSE ≤14, compared with 18.3% of mild-to-moderate AD patients.

Of note, an aggressive reaction was rarely reported, with incidences of 1.4% in the ADAS-cog >30 subgroup and 0% in the MMSE ≤14 subgroup. This supports findings from a 6-month analysis of these pooled data sets [16], where agitation was observed in fewer patients with galantamine (7.3–14.3%) than in control placebo groups (16.0–26.2%). Moreover, the incidence of agitation did not increase with prolonged treatment in the current study; agitation occurred in 7.7–14.5% of patients after 12 months of galantamine treatment in 'advanced moderate' AD patients, which is comparable to rates seen in the overall mild-to-moderate patient group (10.5%). Sleep disturbances such as abnormal dreams and insomnia were also rare. Abnormal dreams occurred in 1.4% of patients in the ADAS-cog >30 subgroup and 0% in the MMSE ≤14 subgroup. Insomnia was seen in 7.2 and 7.7% of patients in these groups, respectively.

Discussion

These data suggest that galantamine is beneficial and well tolerated in patients with 'advanced moderate' AD and that benefits are maintained for at least 12 months. Galantamine maintained cognitive abilities at baseline levels, while matched patients in the historical placebo cohort deteriorated significantly. Functional abilities were significantly improved in patients receiving galantamine compared with those in the historical placebo group. The efficacy of galantamine observed in these patients with 'advanced moderate' AD is at least as great as that observed in patients with mild-to-moderate disease – considering recent findings that the cholinergic deficit is greater in moderate than in mild AD patients, this outcome is not surprising.

The relevance of the historical placebo data used in this analysis is illustrated by the observation that the 6-month data fit closely with the recent published data from 6-month trials [2–5]. The historical placebo declines observed on the ADAS-cog and DAD scales were greater than those observed in the original studies, in which patients with mild-to-moderate AD declined on the ADAS-cog by 6 points and on the DAD by 11–13 points [9, 12]. In contrast, the historical controls with 'advanced

moderate' AD declined by about 9–10 points on the ADAS-cog and about 20 points on the DAD. Galantamine offers consistent, sustained efficacy, regardless of baseline disease severity. Other analyses in patients with 'advanced moderate' AD have demonstrated that galantamine offers significant improvements over placebo and baseline in cognitive and functional abilities for 6 months, and delays the emergence of behavioural symptoms for at least 5 months [17].

The recent NICE guidance recommended that cholinergic treatments should be made available to patients with mild-to-moderate AD [10]. From a practical viewpoint, clinicians also need to know how to treat patients with more advanced disease. The NICE recommended that treatment with cholinesterase inhibitors should not be initiated in patients with MMSE ≤ 12, since there was no evidence that they would benefit in a meaningful way. Unfortunately, there were too few patients in the original study population to perform an analysis of patients with a baseline MMSE ≤ 12, although the mean baseline MMSE score in the patients used for this post hoc analysis was 12.5. Our analysis demonstrates that patients with low MMSE or high ADAS-cog scores experience significant, sustained, clinically relevant benefits upon starting galantamine treatment.

Long-term galantamine treatment appeared to be well tolerated in patients with 'advanced moderate' AD. As expected, the most frequent side-effects were cholinergic gastro-intestinal effects. However, nausea appeared to be reported less frequently in this study of 'advanced moderate' AD patients compared with the overall database of patients with mild-to-moderate illness (10–20% lower incidence). This suggests that nausea may be less problematic in 'advanced moderate' AD patients than in those with mild-to-moderate disease. There was a slight increase in the incidence of diarrhoea relative to the mild-to-moderate AD group, but the 2–7% higher rates seen in 'advanced moderate' AD patients were not considered to represent a clinically relevant difference in tolerability. Agitation was rarely reported, possibly reflecting the positive effect that galantamine has on delaying behavioural symptoms [3]. Sleep disorders such as insomnia are a common feature of AD, and prolonged use of conventional acetylcholinesterase inhibitors has been associated with increased incidence of sleep disruption and more frequent use of sleep-related medications [18–20]. However, there was no evidence in this study of adverse events relating to excessive sleep disturbance with the use of galantamine in these patients. This supports the findings from previous studies showing that galantamine does not adversely affect sleep [21, 22]. Furthermore, it is known that the tolerability profile of galantamine may be further optimized by using the recommended 4-weekly dose escalation scheme [3]. In the two 12-month pivotal studies used for this pooled analysis, a faster dose escalation scheme of galantamine was used.

We conclude that patients with AD may continue to experience efficacy benefits of clinical value from maintained, long-term galantamine treatment, even into more advanced disease. Galantamine also appears to be well tolerated in patients with 'advanced moderate' disease. Whether this reflects the dual mode of action of galantamine is not known at present. Further clinical experience should help in confirming that galantamine has potential for use in a broader clinical population than that evaluated during pivotal clinical trials.

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