

Efficacy and safety of galantamine in patients with mild to moderate Alzheimer's disease: multicentre randomised controlled trial

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Abstract

Objective To evaluate the efficacy and safety of galantamine in the treatment of Alzheimer's disease.

Design Randomised, double blind, parallel group, placebo controlled trial.

Setting 86 outpatient clinics in Europe and Canada.

Participants 653 patients with mild to moderate Alzheimer's disease.

Intervention Patients randomly assigned to galantamine had their daily dose escalated over three to four weeks to maintenance doses of 24 or 32 mg.

Main outcome measures Scores on the 11 item cognitive subscale of the Alzheimer's disease assessment scale, the clinician's interview based impression of change plus caregiver input, and the disability assessment for dementia scale. The effect of apolipoprotein E4 genotype on response to treatment was also assessed.

Results At six months, patients who received galantamine had a significantly better outcome on the 11 item cognitive subscale of the Alzheimer's disease assessment scale than patients in the placebo group (mean treatment effect 2.9 points for lower dose and 3.1 for higher dose, intention to treat analysis, $P < 0.001$ for both doses). Galantamine was more effective than placebo on the clinician's interview based impression of change plus caregiver input ($P < 0.05$ for both doses *v* placebo). At six months, patients in the higher dose galantamine group had significantly better scores on the disability assessment for dementia scale than patients in the placebo group (mean treatment effect 3.4 points, $P < 0.05$). Apolipoprotein E genotype had no effect on the efficacy of galantamine. 80% (525) of patients completed the study.

Conclusion Galantamine is effective and well tolerated in Alzheimer's disease. As galantamine slowed the decline of functional ability as well as cognition, its effects are likely to be clinically relevant.

Introduction

Cholinergic deficits are the most prominent neurochemical disturbances in patients with Alzheimer's disease and are thought to contribute to the deterioration in memory and other cognitive functions.¹ Several pharmacological approaches have been used in an attempt to correct these deficits.² Of these strategies, inhibition of acetylcholinesterase is currently the most successful treatment for Alzheimer's disease.³ Well designed clinical trials have consistently shown improved cognition and global assessment scores in patients taking acetylcholinesterase inhibitors.^{3,4} The effects of cholinesterase inhibitors on patients' activities of daily living are unclear.^{5,6} There is also

some evidence that patients who have the apolipoprotein E4 genotype may have a reduced response to cholinesterase inhibitors.^{7,8}

Galantamine is a new drug that reversibly and competitively inhibits acetylcholinesterase^{9,10} and enhances the response of nicotinic receptors to acetylcholine.¹¹

We evaluated the efficacy and safety of two maintenance doses of galantamine over six months compared with placebo in patients with mild to moderate Alzheimer's disease. We also investigated whether the apolipoprotein E4 genotype influences the response to galantamine.

Participants and methods

We studied outpatients who had a history of cognitive decline that had been gradual in onset and progressive over at least six months. Participants had to meet the criteria for probable Alzheimer's disease¹² and to have mild to moderate dementia, defined as a score of 11-24 on the mini-mental state examination¹³ and a score of ≥ 12 on the 11 item cognitive subscale of the Alzheimer's disease assessment scale.¹⁴ Patients had to live with, or be visited at least five days a week by, a responsible caregiver. Patients with concomitant diseases were included in the study provided that their illness was controlled.

Patients were excluded from the study if they had any other neurodegenerative disorder; multi-infarct dementia or clinically active cerebrovascular disease; cardiovascular disease thought likely to prevent completion of the study; clinically important cerebrovascular, psychiatric, hepatic, renal, pulmonary, metabolic, or endocrine conditions or urinary outflow obstruction; an active peptic ulcer; or any history of epilepsy or serious drug or alcohol misuse. We also excluded patients who had been treated for Alzheimer's disease with a cholinesterase inhibitor. A blood sample was taken at baseline for apolipoprotein E genotyping.¹⁵

The caregiver together with the patient (or their relative, guardian, or legal representative) provided written informed consent to participate in the study. The trial was performed in accordance with the Declaration of Helsinki and its subsequent revisions and approved by ethics committees at each centre.

Design

This was a six month, parallel group, double blind, placebo controlled trial undertaken in 86 centres in eight countries (Canada, Finland, France, Germany, Norway, Sweden, the Netherlands, and the United Kingdom). Patients were randomly assigned to one of two galantamine treatment groups or a placebo group by simple computer generated randomisation. In both

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galantamine groups, the galantamine regimen was 8 mg daily for one week, increasing to 16 mg daily for the second week and to 24 mg daily for the third week. In the fourth week, one galantamine group continued on 24 mg while the other group had the dose increased to 32 mg daily.

The primary efficacy variables used in the trial were the standard 11 item cognitive subscale of the Alzheimer's disease assessment scale (score range 0-70; higher scores indicate greater cognitive impairment)¹⁴ to assess cognitive function (memory, attention, language, orientation, etc) and the clinician's interview based impression of change plus caregiver input,¹⁶ which provides a global impression of a patient's improvement or deterioration over the course of the

illness. The clinician's interview was scored relative to baseline by a clinician blinded to other assessments and was based on separate interviews with the patient and the caregiver. The primary end point was at six months.

A secondary efficacy variable was the disability assessment for dementia scale, based on an interview with the caregiver, to assess activities of daily living (self care activities, instrumental (complex) activities of daily living, planning and organisation, leisure, effective performance, initiation). The disability assessment scale uses 46 questions and has a score range of 0-100 (higher scores indicate better functioning).¹⁷ Details of other secondary efficacy variables are available on the *BMJ's* website.

Safety evaluations throughout the study comprised regular physical examinations, electrocardiography, measurements of vital signs, standard laboratory tests, and monitoring for adverse events.

Statistical analysis

We estimated that we needed about 180 patients in each treatment group to achieve 80% power ($\alpha=0.025$ with a Bonferroni adjustment) to detect a 2.75 point change. This difference in the change in the 11 item cognitive subscale of the Alzheimer's disease assessment scores between patients who received galantamine and placebo after six months was considered to be clinically meaningful.

All randomised patients who took at least one dose of the trial drug were included in the analyses of baseline characteristics and safety data. We performed a six month intention to treat analysis that included all randomised patients who had any efficacy assessment, whether at baseline or during treatment. The last available assessment was carried forward into all subsequent assessment times for which actual data were not available.

We used the following methods to compare variables between each galantamine group and the placebo group: analysis of variance, using treatment and country as factors; generalised Cochran-Mantel-Haenszel test, controlling for country, for response rates to the 11 item cognitive subscale of the Alzheimer's disease assessment scale; and Van Elteren test,¹⁸ controlling for country, for the clinician's interview based impression of change plus caregiver input. The time-response relation for change in the 11 item cognitive subscale of the Alzheimer's disease assessment scale was analysed by generalised linear mixed modelling. All tests were evaluated at the 5% significance level. The statistical software used was SAS version 6.12.

Results

Of the 753 patients screened for the study, 653 were randomised to treatment (fig 1). The baseline characteristics of the three treatment groups were comparable (table 1).

Primary efficacy variables

At six months, patients who received galantamine had significantly better cognitive function than patients in the placebo group (table 2). The difference in mean change from baseline score increased progressively over time ($P<0.0001$ for both doses) (fig 2).

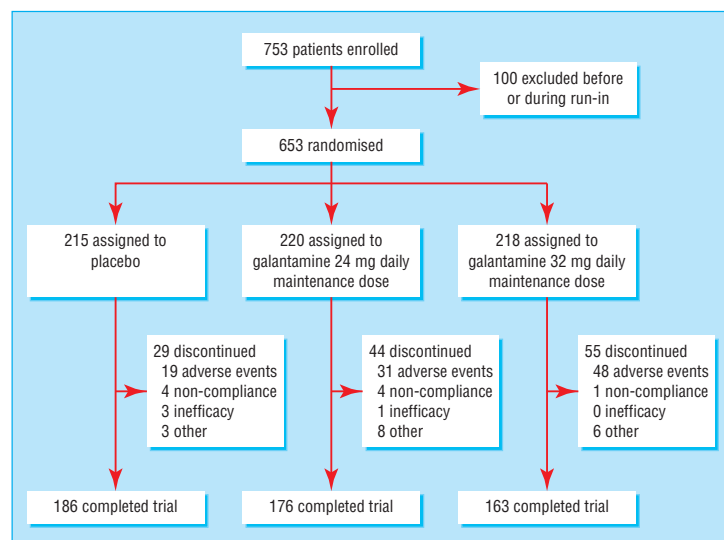


Fig 1 Profile of trial

Table 1 Baseline characteristics of participants. Values are numbers (percentages) unless stated otherwise

Characteristic	Placebo (n=215)	Galantamine 24 mg (n=220)	Galantamine 32 mg (n=218)
Demography			
Men/women	83/132	81/139	80/138
Mean (SD) age (years)	72.7 (7.6)	71.9 (8.3)	72.1 (8.6)
Clinical			
Mean (SD) weight (kg)	67.2 (12.1)	66.7 (12.8)	66.2 (13.4)
No (%) of smokers	193 (90)	200 (91)	199 (91)
Other active medical conditions	154 (72)	159 (72)	168 (77)
No (%) with apolipoprotein E4 allele*			
Homozygous	34 (18)	32 (17)	27 (15)
Heterozygous	83 (45)	97 (53)	95 (53)
Mean (SD) mini-mental state examination score	19.3 (3.5)	19.5 (3.4)	19.0 (3.8)
Mean (SD) Alzheimer's disease assessment scale score†	24.7 (9.3)	25.4 (9.4)	26.2 (10.4)
Mean (SD) disability assessment in dementia score	66.6 (22.5)	69.9 (21.4)	69.6 (20.6)
Mean (SD) time since cognitive problem diagnosed (years)	3.5 (2.3)	3.6 (2.7)	3.7 (2.2)
Mean (SD) time since probable Alzheimer's disease diagnosed (years)	0.8 (1.0)	0.9 (1.2)	0.8 (1.0)
Brain imaging findings‡			
Territorial infarctions	1 (0.5)	7 (3)	2 (1)
Lacunar infarctions	17 (8)	10 (5)	16 (7)
White matter lesions	0	0	2 (1)
Tumour	0	1 (0.5)	1 (0.5)

*n=185 for placebo, n=184 for galantamine 24 mg, and n=179 for galantamine 32 mg.

†11 item cognitive subscale.

‡Computed tomography or magnetic resonance imaging findings in past 12 months.

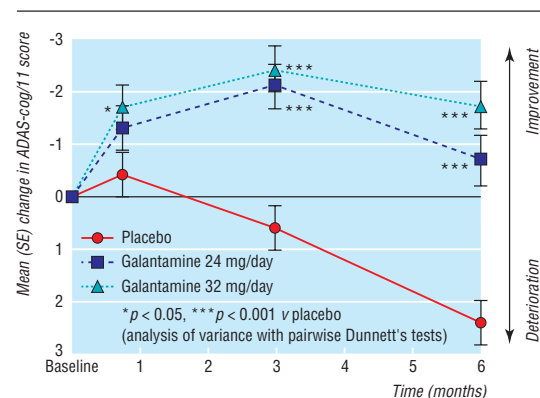
Table 2 Change from baseline in measures of efficacy at six months, intention to treat analysis

Efficacy measure	Placebo	Galantamine 24 mg	Galantamine 32 mg	Treatment difference (95% CI)*	
				Galantamine 24 mg	Galantamine 32 mg
11 item cognitive subscale of Alzheimer's disease assessment scale†					
No of patients	215	220	217		
Mean (SE) change from baseline	2.4 (0.41)	-0.5 (0.38)	-0.8 (0.43)	2.9 (1.6 to 4.1) P<0.001	3.1 (1.9 to 4.4) P<0.001
No (%) with ≥0 points improvement	88 (41)	138 (63)	130 (60)	21.5 (12.0 to 31.0) P<0.001	19.5 (10.0 to 29.0) P<0.001
No (%) with ≥4 points improvement	32 (15)	64 (29)	70 (32)	14.0 (6.0 to 22.0) P<0.001	17.0 (9.0 to 25.0) P<0.001
Disability assessment for dementia score‡					
No of patients	210	212	214		
Mean (SE) change from baseline	-6.0 (1.08)	-3.2 (1.02)	-2.5 (1.07)	2.8 (-0.6 to 6.1) P=0.1	3.4 (0.1 to 6.7) P<0.05
Clinician's interview based impression of change plus caregiver input					
No (%) of patients	203	206	198		
1=Much improved	0	0	0		
2=Moderately improved	1 (0.5)	7 (3)	9 (5)		
3=Minimally improved	32 (16)	29 (14)	39 (20)		
4=No change	68 (33)	91 (44)	82 (41)	<0.05§	<0.001§
5=Minimally worsened	68 (33)	57 (28)	54 (27)		
6=Moderately worsened	32 (16)	17 (8)	14 (7)		
7=Much worsened	2 (1)	5 (2)	1 (1)		

*Difference from placebo.

†Negative change from baseline indicates improvement.

‡Negative change from baseline indicates deterioration.

§Van Elteren test was used to test for differences in the distribution of scores between placebo and galantamine groups. For details of the observed case analysis see table 2 on *BMJ's* website.**Fig 2** Mean (SE) change from baseline in score on 11 item cognitive subscale of Alzheimer's disease assessment scale over time, observed case analysis

Galantamine produced a better outcome than placebo on the 11 item cognitive subscale of the Alzheimer's disease assessment scale regardless of the number of copies of the E4 apolipoprotein allele that a patient had (table 3).

The effect of either dose of galantamine on the clinician's interview based impression of change plus caregiver input ratings was significantly better than that of placebo at six months (table 2).

After six months of treatment, the higher dose of galantamine also produced a significantly better outcome on the disability assessment for dementia scale than placebo (table 2).

Safety

At least 5% more patients in the galantamine group than in the placebo group reported nausea, vomiting, diarrhoea, dizziness, headache, anorexia, and weight loss, with nausea being the most common adverse event (table 4). Most adverse events (92%) were mild to moderate in severity, and the proportion of serious

adverse events was similar in the three treatment groups (12-13%).

Discontinuations due to adverse events were more common in patients who received galantamine (18% (79/438)) than in patients in the placebo group (9% (19/215), fig 1). More patients in the higher dose group (22% (48/218)) discontinued treatment because of adverse events than in the lower dose group (14% (31/220)). The events most commonly associated with discontinuation from galantamine treatment were nausea and vomiting. About half of the patients who discontinued due to adverse events during galantamine treatment (43/79) stopped during the dose escalation phase.

Table 3 Change from baseline in score on 11 item cognitive subscale of Alzheimer's disease assessment scale at six months according to apolipoprotein E genotype

No of copies of E4 allele	Placebo group		Galantamine groups		P value
	No of patients*	Mean (SE) change	No of patients*	Mean (SE) change	
Two	27	5.1 (1.1)	48	-1.5 (0.7)	0.0001
One	67	1.9 (0.6)	138	-1.0 (0.5)	0.0008
None	56	2.1 (0.9)	78	-1.7 (0.7)	0.0006

*The low patient numbers reflect the fact that many patients did not give informed consent for apolipoprotein E genotyping.

Table 4 Adverse events for which the difference between the galantamine and placebo groups was at least 5%. Values are numbers (percentages) of patients

Adverse event	Placebo group (n=215)	Galantamine 24 mg (n=220)	Galantamine 32 mg (n=218)
Nausea	26 (12)	82 (37)	87 (40)
Vomiting	9 (4)	45 (20)	37 (17)
Diarrhoea	16 (7)	16 (7)	29 (13)
Dizziness	10 (5)	24 (11)	26 (12)
Headache	7 (3)	21 (10)	25 (11)
Anorexia	0	22 (10)	23 (11)
Weight loss	1 (0.5)	17 (8)	11 (5)
Any adverse event	165 (77)	182 (83)	194 (89)

What is already known on this topic

Alzheimer's disease is characterised by a progressive decline in patients' cognitive function and ability to perform daily activities

Acetylcholinesterase inhibitors have been shown to improve cognitive function in patients with Alzheimer's disease

It is unclear whether changes in cognitive function, as measured on a psychometric scale, translate into clinically important outcomes for patients and their carers

What this study adds

Galantamine significantly improved cognitive function relative to placebo over six months

Treatment also slowed the progression of functional decline

The beneficial effect was evident in patients with and without the apolipoprotein E4 allele

Discussion

Our study shows that, compared with placebo, galantamine significantly improved cognition and global function in patients with mild to moderate Alzheimer's disease. These therapeutic effects were associated with significant benefits on patients' activities of daily living.

Effects of other cholinesterase inhibitors

The effects of traditional cholinesterase inhibitors on activities of daily living are unclear.⁵ Metrifonate was shown to have functional benefits in a six month study that used the disability assessment for dementia scale.¹⁹ Studies on donepezil have either not reported functional benefits²⁰⁻²² or have shown benefit if basic activities of daily living (self care tasks such as dressing and personal hygiene) are removed from the analysis.²³ Rivastigmine was also shown to have favourable effects on daily activities,^{24 25} although the validity of these results has been questioned.⁶

The decline in both cognitive functions and activities of daily living in the placebo group in our study was at least as great as that found in placebo groups in other comparable studies.²²⁻²⁵ These data suggest that galantamine's cognitive and functional benefits are unlikely to be due to the inclusion of patients with less severe disease.

As many as 70% of patients with Alzheimer's disease carry at least one copy of apolipoprotein E4.²⁶ These patients seem to have a greater impairment of presynaptic cholinergic function than patients without the apolipoprotein E4 allele, which might be expected to reduce their response to treatment. However, galantamine significantly improved cognitive function, relative to placebo, regardless of patients' apolipoprotein E genotype. These findings contrast with results for tacrine⁸ but agree with a recent pooled analysis of metrifonate studies.²⁷

Side effects

Galantamine was well tolerated by most patients. The completion rates for the two galantamine groups were comparable to those reported for other cholinesterase inhibitors.²²⁻²⁵ More adverse events were reported with the higher dose, and more patients who received the

higher dose discontinued treatment due to adverse events. The most common adverse event in the galantamine groups was nausea, which has also been reported with other cholinesterase inhibitors.^{22 23 25} For most patients in our study, nausea was mild to moderate and lasted a median of five to six days.

The monthly rate of discontinuations due to adverse events with galantamine was comparable to the rate with placebo during the maintenance phase of the study, suggesting that the rapid, rigid dose escalation procedure may have contributed to patients discontinuing galantamine treatment. In a recent, five month, placebo controlled study of galantamine, in which the dose was escalated over eight weeks, the proportion of patients who discontinued galantamine 24 mg/day due to adverse events was low (10%) and comparable to that in the placebo group (7%).²⁸ In clinical practice, patients' tolerance of galantamine might be improved by starting at a low dose and escalating the dose slowly.

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Canada: Addington D, Ancill R, Bergman H, Campbell B, Feldman H, Hutchings R, McCracken P, McKelvey R, Mohr E, Nair V, Naranjo C, Rabheru K, Rajput A, Robillard A, Van Reekum R, Veloso F.

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Contributors: GKW and SL participated in the design and execution of the study as well as analysis of data and writing the paper. EG participated in analysing and interpreting the data and writing the paper. GKW will act as the guarantor for the paper.

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Competing interests: GKW's department receives research support from Shire Pharmaceuticals Group and Janssen Pharmaceutica, who have codeveloped galantamine. GKW has received consultancy fees from Shire Pharmaceuticals Group and Janssen Pharmaceutica.

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Drug points

Recurrent generalised urticaria at insulin injection sites

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In July 1998 a six year old boy with insulin dependent diabetes presented one year after diagnosis with an urticarial rash involving all insulin injection sites. The pruritic rash started 10 minutes after injection of human Mixtard 30 (Novo Nordisk) in the arm. He was otherwise well. The rash occurred at injection sites on the arms, thighs, and buttocks (not used for two months), which disappeared spontaneously within 12 hours. Subsequently in September 1998 (figure), December 1998, and February 1999 he had milder episodes soon after insulin injection. When the insulin was changed to Humulin M3 (Lilly) he had three urticarial reactions in the first two weeks and further reactions in September 1999 and April 2000. The mean insulin dose was 0.61 units/kg/day. There was no history of atopy.

His mean haemoglobin A1c was 8.0%, and the blood count was normal. Tests for insulin specific IgE gave negative results but there was a high titre for insulin specific IgG. Tests for reactions to the constituents of Humulin M3 and Mixtard 30 were not performed.

The Committee on Safety of Medicines has received one report of rapid onset itching and erythema at all previous injection sites. This concerned a 68 year old woman treated with Protophane (now called Insulatard; Novo Nordisk), Velosulin (Novo Nordisk), and enalapril.

To my knowledge this is the first published report in a child of a human insulin preparation causing intermittent urticaria simultaneously affecting only previous injection sites. The boy had never received animal insulin and there had been no interruption in his treatment. Mixtard 30 and Humulin M3 are identical in composition (human insulin, m-cresol, zinc oxide, sodium hydroxide, hydrochloric acid, sodium phosphate, phenol, and protamine) except for



Urticarial rash on buttocks. Reproduced with parents' permission

glycerol in Humulin M3. It seems likely that this reaction was mediated by insulin specific IgE fixed in mast cells located at insulin injection sites. Zinc allergy is unlikely as it is associated with delayed reactions.¹ Reaction to protamine is another possible explanation, with intermittent rash occurring as a result of variation in protamine concentration owing to incomplete mixing in the injection device.^{2,3}

This rare insulin reaction initially caused major concern because of the uncertain prognosis. Two years after onset any urticarial rashes are treated by the boy's parents with antihistamine (chlorpheniramine).

Competing interests: None declared.

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