Effect of Galantamine Hydrobromide in Chronic Fatigue Syndrome

A Randomized Controlled Trial

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Context There is no established pharmacological treatment for the core symptoms of chronic fatigue syndrome (CFS). Galantamine hydrobromide, an acetyl cholesterone inhibitor, has pharmacological properties that might benefit patients with CFS.

Objective To compare the efficacy and tolerability of galantamine hydrobromide in patients with CFS.

Design, Setting, and Patients Randomized, double-blind trial conducted June 1997 through July 1999 at 35 outpatient centers in the United Kingdom (n=17), United States (n=14), the Netherlands (n=2), Sweden (n=1), and Belgium (n=1) involving 434 patients with a clinical diagnosis of CFS (modified US Centers for Disease Control and Prevention criteria).

Interventions A total of 89 patients were randomly assigned to receive 2.5 mg of galantamine hydrobromide; 86 patients, 5.0 mg; 91 patients, 7.5 mg; and 86 patients, 10 mg (these patients received medicine in the tablet form 3 times per day); a total of 82 patients received matching placebo tablets 3 times per day.

Main Outcome Measures The primary efficacy variable was the global change on the Clinician Global Impression Scale after 4, 8, 12, and 16 weeks of treatment. Secondary outcomes were changes in core symptoms of CFS on the Chalder Fatigue Rating Scale, the Fibromyalgia Impact Questionnaire, and the Pittsburgh Sleep Quality Index; changes in quality of life on the Nottingham Health Profile; and assessment of plasma-free cortisol levels and cognitive performance on a computer-based battery of tests.

Results After 16 weeks, there were no statistically significant differences between any of the galantamine or placebo groups in clinical condition on the Clinician Global Impression Scale, or for any of the secondary end points. Exploratory regression analysis failed to detect any consistent prognostic factor that might have influenced the primary or any secondary outcome measures.

Conclusion This trial did not demonstrate any benefit of galantamine over placebo in the treatment of patients with CFS.

JAMA. 2004;292:1195-1204 www.jama.com

CHRONIC FATIGUE SYNDROME (CFS) is a complex disorder characterized by long-term disability. The rate of spontaneous recovery in CFS is low[1] and no consistently effective treatment is available. Hypoactivity of the hypothalamic-pituitary-adrenal axis has been demonstrated in some patients with CFS and fibromyalgia.[2-7] Some evidence suggests that CFS patients may have enhanced sensitivity of the peripheral cholinergic vascular system and an exaggerated pyridostigmine-stimulated growth hormone release response.[8] Acetylcholine is implicated in vagal tone, baroreceptor reflexes, and in transmission at the nicotinic sympathetic ganglia and at the neuromuscular junctions. Patients with CFS are often intolerant of the anticholinergic adverse effects of tricyclic antidepressants and these symptoms are similar to the symptoms of CFS. The frequent complaint of cognitive impairment in CFS also is consistent with the cholinergic hypothesis of cognition.

For editorial comment see p 1234.

A functional deficiency of cholinergic neurotransmission offers one possible explanation for the findings of a hypoactive hypothalamic-pituitary-adrenal axis; under conditions of stress, acetylcholine facilitates the release of corticotrophin-releasing hormone. Cholinergic stimulation also releases

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Financial Disclosure: Dr Blacker received research support from Shire Pharmaceutical Development Ltd.
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growth hormone with consequent increases in levels of insulin-like growth factor I, which plays an important role in the regenerative functions of the peripheral nerves and skeletal muscles.[9] In addition, sleep disturbances are commonly reported in patients with CFS, and it has been proposed that a disturbance of slow wave sleep, an increase in rapid eye movement (REM), sleep latency, and prolongation of REM sleep with diminished REM density may be indicative of a central cholinergic deficiency. In animal models, the triggering and maintenance of REM sleep has been shown to be under the control of cholinergic neurons; in humans, cholinergic agonists or cholinesterase inhibitors lead to an earlier onset of REM sleep.[10,11]

Galantamine hydrobromide is a selective, reversible, inhibitor of acetylcholinesterase that is active both peripherally and in the central nervous system by virtue of its ability to cross the blood-brain barrier. Galantamine is also an allosteric modulator that enhances the effects of acetylcholine at cholinergic nicotinic receptors.

Galantamine was first introduced clinically as an anticurare agent and has been used to treat Alzheimer disease,[12,13] various neurological disorders,[14] and mania.[15] When given intravenously, this agent rapidly increases plasma cortisol levels.[16] Additionally, galantamine decreases REM sleep latency and increases REM density.[11] Thus, several pharmacological properties of galantamine might potentially benefit patients with CFS; a previous pilot trial with CFS patients suggested that the drug might be therapeutic.[17]

METHODS

Study Design

In this multicenter, randomized, double-blind, placebo-controlled trial conducted June 1997 through July 1999, patients with CFS were randomly assigned to 1 of 5 treatment groups to receive galantamine hydrobromide or matching placebo. Randomization was in balanced blocks of 5 patients (1:1:1:1:1 ratio) according to a schedule produced using SAS statistical software (version 6.12, SAS Institute Inc, Cary, NC). Patients who satisfied all entry criteria at the randomization visit were assigned at each center the next available (lowest) patient (randomization) number.

The trial comprised an initial 2-week screening period after which patients were randomized to receive galantamine or placebo—the doses of which were both increased by gradual titration over 3 to 8 weeks followed by maintenance treatment at the target dose for a total of 16 weeks. The 16-week trial duration was chosen due to the fluctuating nature of CFS; the need to allow adequate time for a dose titration to minimize patient withdrawal in case of nausea (based on experiences with galantamine in Alzheimer patients); and to allow time for sufficient exposure to the highest dose. Assessment visits were scheduled at 4-week intervals with a follow-up assessment at 4 weeks after the final dose. In the event of early withdrawal, 2 final assessments took place: 4 weeks after the last dose of medication and again at the originally scheduled end of treatment (week 16).

Between-center comparisons were planned from the outset on the basis of potential sample differences between clinic types (rheumatology, neurology, psychiatry, immunology, and miscellaneous). A separate analysis also was planned to compare the United States with other countries.

Patient Selection

Eligibility requirements included age between 18 and 65 years, modified US Centers for Disease Control and Prevention diagnosis for CFS,[18] and illness duration of less than 7 years. Patients with a primary diagnosis of fibromyalgia (defined by the American Rheumatologic Association criteria[19]) were eligible if they also fulfilled the US Centers for Disease Control and Prevention modified criteria. The majority of the study participants were recruited from primary care sources; a few came from tertiary referral centers. Patients were excluded if they had any of the following concurrent *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* psychiatric diagnoses: major depressive disorder, psychotic disorders, panic disorder, substance misuse, somatization disorder, anorexia or bulimia nervosa, obesity, and sleep disorders. Patients were also excluded if they had received inpatient psychiatric care, had previously attempted suicide, or had both. Other exclusions included irritable bowel syndrome, peptic ulcer, severe asthma, endocrine or metabolic disease, human immunodeficiency virus infection, neurological disease (eg, epilepsy or multiple sclerosis), known sensitivity to cholinergic agents, possible exposure to organophosphate compounds, or a diagnosis of Gulf War syndrome. Pregnant or lactating women and women with menstrual irregularities associated with fatigue were excluded. Women of childbearing potential required a negative pregnancy result before randomization and were requested to use a barrier method of contraception throughout the trial (in addition to any oral contraception). Participation in cognitive behavioral therapy or graded exercise programs was not permitted during the study.

Except for the occasional use of minor analgesics (eg, paracetamol/acetaminophen and aspirin), no concomitant medication was allowed. Patients taking antidepressant drugs were required to discontinue use within a minimum of 12 weeks before randomization. Patients taking any other psychotropic medication were required to discontinue use 6 weeks prior to randomization. Patients were not allowed to take the following drugs within 3 months prior to enrollment: cholinergic agonist or antagonist properties, antihypertensives, drugs interfering with neuromuscular transmission, corticosteroids, antihistamines, or any other investigational drugs. Because the most likely unwanted effect of galantamine was anticipated to be nausea, a nonantimuscarinic antiemetic (domperidone) was permitted and sometimes was required.

All patients were provided with an information leaflet about the study and encouraged to take the information home and discuss the trial with their family. All patients were given the opportunity to ask questions and to receive adequate responses prior to providing consent for the study. Investigators in the United States and Europe indicated a patient's ethnicity from a list containing "white, black, Indian subcontinent, Asian, Hispanic, other (specify)." All patients provided written informed consent.

Ethics approval was obtained locally at each site before any patients were screened. The investigators at each site were responsible for obtaining ethics approval. Regulatory approval was obtained by the study sponsor in each country that required it according to local regulations.

Interventions

Following an initial 2-week screening period, patients were randomly assigned to receive identical tablets of placebo or 1 of 4 doses of galantamine hydrobromide 3 times per day (2.5 mg [7.5 mg/d]), 5 mg [15 mg/d], 7.5 mg [22.5 mg/d], or 10 mg [30 mg/d]). Patients had their medication dose titrated over a 3- to 8-week period, commencing at 2.5 mg/d with weekly increments of between 2.5 mg and 7.5 mg depending on the target dose, which was then maintained for another 8 weeks. The total duration of treatment was 16 weeks.

Main Outcome Measures

There is no generally accepted instrument for reliably measuring the severity or change in symptoms of CFS. However, the Clinician Global Impression (CGI) Scale has proven validity and reliability in the measurement of change and is extensively used in therapeutic trials.[20] Furthermore, an analytical review of 24 controlled trials in fibromyalgia advocated the use of the CGI Scale as the most sensitive and appropriate instrument for the assessment of change in this closely related condition.[21] We adopted the CGI Scale as the primary measure of outcome (a score of zero indicated very much improved; 1, much improved; 2, minimally improved; 3, no change; 4, minimally worse; 5, much worse; and 6, very much worse). Following recommendations by the UK Medicines Control Agency, the outcome categories were dichotomized for analyses into response or no response in which the scores of zero and 1 were combined to define a positive patient response while all other scores of 2 through 6 were defined as a nonresponse to treatment. This was on the advice of the investigators who were primarily interested in detecting a change that was clinically significant.

Secondary outcome measures focused on change in fatigue intensity, functional impairment, sleep and quality of life using the Chalder Fatigue Rating Scale,[22] the Fibromyalgia Impact Questionnaire,[23] the Pittsburgh Sleep Quality Index,[24] and the Nottingham Health Profile.[25] Cognitive function was assessed with a computerized assessment system (Cognitive Drug Research Ltd, Reading, England).

This computerized assessment system has been extensively validated and used in worldwide clinical trials since the mid-1980s. It consists of a series of computer-administered cognitive tasks, which assess core aspects of attention, working, and episodic secondary memory. The tests are highly sensitive to cholinergic compounds and can detect the effects of anticholinesterases including galantamine in individuals with dementia.[26-33] The selection of tests used in this study (simple and choice reaction time, digit vigilance, articulatory and spatial working memory, immediate and delayed word recall, and word and picture recognition) has been described in detail previously[31] and took between 20 and 25 minutes to perform. The information is presented on computer monitors and the patients respond by pressing either a "yes" or "no" button on a response module. Parallel forms of the tests are automatically selected by the system and presented at each testing session. Each patient underwent 2 training sessions on the tests during screening. The same test administrators oversaw the computerized cognitive assessment at each visit and at the same time of day throughout the study

Plasma-free cortisol was measured at baseline and after 8, 12, and 16 weeks of treatment. Fasting blood samples for cortisol were obtained at 10:00 AM (±1 hour). For female patients, cortisol assessments were performed on days 1 through 7 of the menstrual cycle, with day 1 defined as the first day of bleeding.

Safety Assessments

Safety assessments included physical and mental examinations, vital signs, hematology studies, and urinalysis. Adverse events were recorded at each assessment. Details of menstrual irregularities (eg, breakthrough bleeding) were also recorded. Mood was monitored throughout using the Beck Depression Inventory; an increase of 6 points or more compared with baseline or a total score of 16 or more at any point during treatment necessitated mandatory withdrawal.

Determination of Sample Size and Statistical Methods

The protocol followed a sequential design that provided for interim analyses of the primary efficacy and safety data; these analyses were conducted at preplanned intervals by an independent data monitoring committee. Interim analyses were conducted after the first 50 patients had completed the 16-week treatment and at intervals of 50 completed patients thereafter. The interim efficacy analyses of the 16-week CGI assessments were based on the intent-to-treat (ITT)–retrieved population. This population included all randomized patients receiving at least 1 dose of study medication. Patients who withdrew prior to week 16, but who were recalled and reassessed at week 16, were included with this week 16 assessment, and those who did not return had their last observation carried forward (LOCF).

At each interim analysis, each galantamine dose was compared with placebo using the lower stopping boundary of the triangular test.[34] The design

had a presumed advantage that any potentially ineffective treatment dose(s) could be identified and randomization of subsequent patients could be optimized. Sample size was calculated to detect a 25% or greater improvement compared with placebo as assessed by the CGI—anything less was considered clinically insignificant.

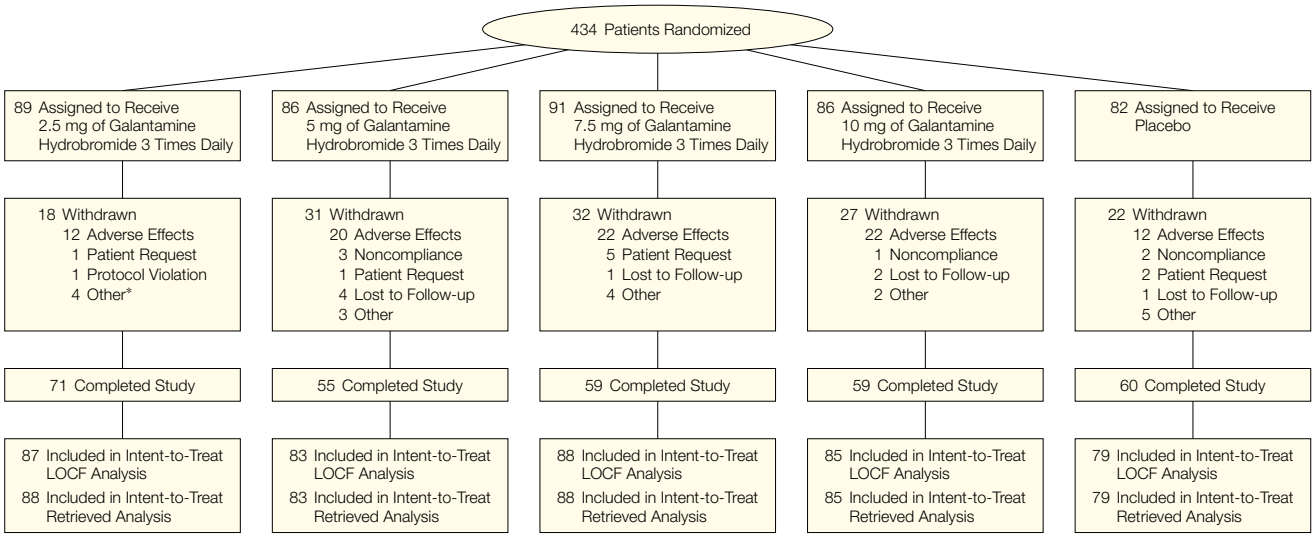
The original sample size assumptions allowed a significance level of 5% (2-tailed) and a power of 90% to detect an improvement in the response rate of 10% with placebo and of 35% with galantamine. Allowance was made for a withdrawal rate of 30%. Sample size assumptions were reviewed at each interim analysis. The target sample size was based on the preliminary power calculations and the second interim analysis of 400 patients (80 per treatment group). The study design was finalized after consultation with independent clinical CFS experts, the UK Medicines Control Agency, and prior to the participation of the US centers, the US Food and Drug Administration.

The primary population for the final analysis was the ITT LOCF population, which was defined as using only the last treatment assessment. Noncompliant patients (those who did not take medication, which was measured by tablet count at each visit) for more than 7 days were permitted to remain in the study as the primary analysis was planned using an ITT population. The final analyses were conducted after all patients had completed the study and were performed on the ITT LOCF and ITT retrieved populations. The models used for the final analysis tested for an overall treatment effect and consisted of 2-sided tests at the 5% significance level. The null hypothesis considered that there was no evidence of a difference in the response rate between any of the galantamine and the placebo treatment groups.

Two analyses of the CGI end point were performed. A logistic regression was used to analyze the percentage of responders. Factors were fitted for treatment and country and the latter were excluded from the model if not statistically significant at the 5% level. The analysis was performed for each analysis population with and without data imputation for missing data. The CGI score at end point was also analyzed using the Cochran Mantel-Haenszel test with modified ridits. In addition to treatment, country (United States vs other countries), and treatment-by-country interaction, potential prognostic factors included in the model were speed of symptom onset (gradual, subacute, or acute), preceding episode of flu (yes or no), duration of illness, and primary symptoms of CFS. All possible terms (covariates, factors, and interactions) were included in the first fitted model. The sequential process consisted of removing the least statistically significant term from the model starting with the interaction terms and then the covariates and factors. The treatment term was forced to remain in the model irrespective of the significance level obtained. In addition, no data imputation was performed in the final exploratory analyses.

Correlation between compliance and CGI response was also investigated. In the main analysis of the secondary efficacy end points, an analysis of variance with type 3 sums of squares was performed at the last patient assessment that complied with the respective analysis population. The model included treatment and country as factors, and investigated the treatment-by-country interaction, which was treated

Figure 1. Flow of Patient Assignment



LOCF indicates last observation carried forward; asterisk, includes 1 patient who was screened and randomized but did not receive study medication because enrollment was closed. Intent-to-treat retrieved analysis indicates values at week 16.

in the same way as in the analysis of the primary end point. The model was applied to each secondary efficacy end point and tested for an overall treatment effect. Statistically significant treatment effects were investigated using Dunnett test accounting for multiple comparisons. Separate treatment comparisons with placebo were made in the event of statistically significant findings. Due to distributional issues for some secondary end points, the data were also analyzed using the Kruskal-Wallis test.

RESULTS

Patient Disposition

A total of 434 patients were recruited from 35 centers (17 in the United Kingdom, 14 in the United States, 2 in the Netherlands, 1 in Sweden, and 1 in Belgium). The patient population and the number of patients included in the analysis populations by treatment group are summarized in FIGURE 1. Patients in the 5 treatment groups were well matched with regard to demographic characteristics (TABLE 1). Of all patients randomized, 304 (70.0%) completed the study and 130 (30.0%) withdrew. A total of 422 patients (97.2%) provided valid data for inclusion in the ITT LOCF population and 423 (97.5%) for inclusion in the ITT retrieved population.

Efficacy Evaluation

Primary End Point. The CGI scores are summarized in TABLE 2 and the differences in percentage of responders compared with placebo during the course of the trial appears in FIGURE 2. Responders were defined as those with CGI scores of zero or 1 (very much or much improved). The difference between galantamine and placebo response rates was, in all instances, less than the prespecified level for clinical significance (25%). Even though more patients were categorized as responders during weeks 12 and 16 in all of the galantamine groups, logistic regression conducted on the ITT LOCF and ITT retrieved populations failed to demonstrate any statistically significant difference between any of the groups. Results from the Cochran Mantel-Haenszel test showed no statistically significant differences in the distribution of patients in the 7 categories of the CGI Scale for both the ITT LOCF and the ITT retrieved populations.

The planned exploratory analysis was performed for all centers with no data imputation to investigate possible influence of the prespecified prognostic factors. None was found to have a statistically significant influence on the CGI of either ITT population. Irrespective of treatment (active drug or placebo), patients who improved during the 16-week double-blind phase exhibited relapse after withdrawal of medication (Table 2). Logistic regression found no significant differences in outcome between the different treat-

Table 1. Demographic Characteristics*

Characteristic	Galantamine Hydrobromide, mg 2.5 (n = 89)	5 (n = 86)	7.5 (n = 91)	10 (n = 86)	Placebo (n = 82)
Sex					
Male	25 (28.1)	25 (29.1)	35 (38.5)	33 (38.4)	31 (37.8)
Female	64 (71.9)	61 (70.9)	56 (61.5)	53 (61.6)	51 (62.2)
Age, y					
≤30	22 (24.7)	25 (29.1)	23 (25.3)	31 (36.0)	21 (25.6)
31-40	24 (27.0)	21 (24.4)	27 (29.7)	24 (27.9)	25 (30.5)
41-50	28 (31.5)	24 (27.9)	23 (25.3)	17 (19.8)	28 (34.1)
>50	15 (16.9)	16 (18.6)	18 (19.8)	14 (16.3)	8 (9.8)
Mean (SD) [range]	39.1 (10.30) [18-57]	38.9 (11.86) [19-64]	39.0 (11.47) [18-60]	37.0 (11.57) [18-67]	37.6 (9.76) [18-56]
Citizenship					
United States	27 (30.3)	29 (33.7)	28 (30.8)	25 (29.1)	24 (29.3)
Other	62 (69.7)	57 (66.3)	63 (69.2)	61 (70.9)	58 (70.7)
Ethnic origin					
White	88 (98.9)	79 (91.9)	89 (97.8)	82 (95.3)	77 (93.9)
Black	1 (1.1)	2 (2.3)	1 (1.1)	1 (1.2)	1 (1.2)
Indian subcontinent	0	1 (1.2)	0	1 (1.2)	0
Asian	0	1 (1.2)	0	0	0
Hispanic	0	3 (3.5)	1 (1.1)	2 (2.3)	3 (3.7)
Unknown	0	0	0	0	1 (1.2)
Weight at screening visit, mean (SD) [range], kg†	71.69 (15.90) [46.0-115.0]	71.21 (16.0) [36.0-115.0]	72.0 (14.68) [45.0-119.5]	69.70 (14.24) [47.7-111.0]	71.20 (12.95) [49.0-99.0]
Height, mean (SD) [range], cm‡	169.5 (10.44) [139-196]	168.8 (12.34) [128-206]	171.1 (10.15) [135-199]	171.1 (9.75) [150-191]	171.0 (8.97) [150-193]

*Values are expressed as number (percentage) unless otherwise indicated.
†Data missing for 1 patient in the placebo group.
‡Data missing for 3 patients in the 2.5-mg galantamine hydrobromide group; 4 in the 5-mg group; 5 in the 7.5-mg group; 4 in the 10-mg group; and 4 in the placebo group.

ment centers (60 for neurology; 24, immunology; 38, rheumatology; 51, infectious disease; 124, psychiatry; and 137, miscellaneous).

Secondary End Points. Observed changes from baseline for the ITT LOCF population for each of the secondary end points after 16 weeks of treatment are summarized in TABLE 3.

Chalder Fatigue Rating Scale. The largest mean improvement was observed in the physical score for patients in the 5-mg galantamine group. However, no significant difference was observed in comparison with placebo. A statistically significant difference was found between the treatment groups in the mental score for both ITT populations with the greatest difference between the 5-mg galantamine group and the other dosage groups. However, no significant difference was observed in comparison with placebo. Patients in the 5-mg galantamine group who reported memory loss had a greater mean improvement in the mental score on the Chalder Fatigue Rating Scale.

Fibromyalgia Impact Questionnaire. At 16 weeks, all but the highest galantamine dose group showed greater mean improvements in the physical and psychological factor scores in comparison with placebo. However, the differences were not statistically significant. For the global well-being factor, all groups exhibited improvements. The greatest mean improvement was in the 5-mg galantamine group, but this was not statistically significant compared with placebo. However, there was, a significant country effect for both ITT populations. The US patients exhibited greater improvement compared with European patients ($P=.01$).

Pittsburgh Sleep Quality Index. There were no statistically significant differences between the galantamine and placebo groups in total Pittsburgh Sleep Quality Index score or any of the various subscale scores. Statistically significant ($P=.002$) country effects were again observed in both the total score and many of the subscale scores. The largest mean improvement from baseline was observed in sleep latency scores in US patients treated with placebo.

Nottingham Health Profile. The greatest mean improvements were observed in the 2.5- and 5-mg galantamine group (part I and part II scales, respectively), but neither group was statistically different from placebo. A country-by-treatment interaction was observed for part II scales ($P=.02$). The greatest mean improvements were observed in European patients in the 2.5-mg galantamine group and in US patients in the 5-mg galantamine group.

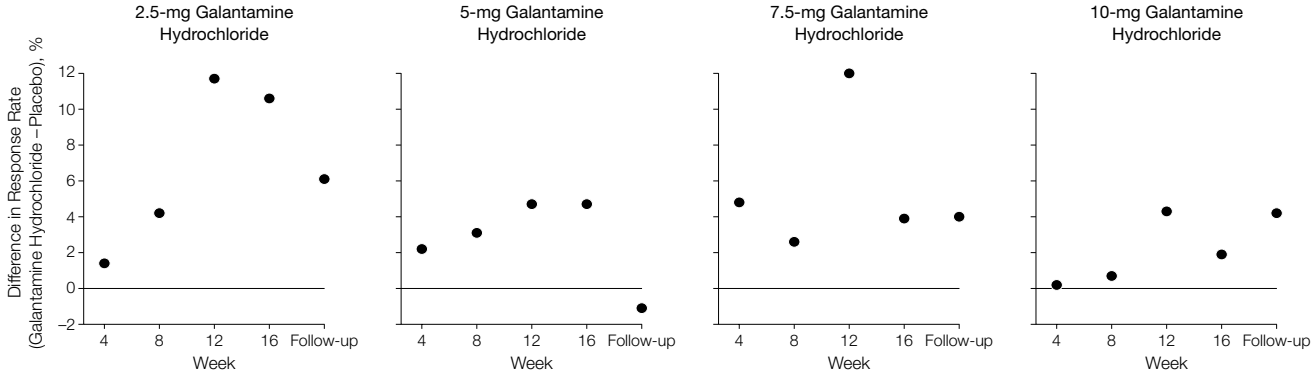
Plasma-Free Cortisol. Plasma levels of cortisol exhibited an overall decrease from baseline in all treatment groups and both ITT populations, the great-

Table 2. Clinician Global Impression Scores*

Global Impression Score	Galantamine Hydrobromide, mg				Placebo
	2.5	5	7.5	10	
Week 4					
0	0	1 (1.3)	1 (1.2)	0	1 (1.3)
1	10 (11.9)	9 (11.4)	12 (14.1)	9 (10.7)	7 (9.2)
2	26 (31.0)	23 (29.1)	23 (27.1)	28 (33.3)	19 (25.0)
3	38 (45.2)	34 (43.0)	34 (40.0)	35 (41.7)	34 (44.7)
4	6 (7.1)	7 (8.9)	12 (14.1)	8 (9.5)	10 (13.2)
5	4 (4.8)	4 (5.1)	3 (3.5)	3 (3.6)	4 (5.3)
6	0	1 (1.3)	0	1 (1.2)	1 (1.3)
Week 8					
0	0	3 (4.2)	4 (5.1)	0	3 (4.5)
1	16 (20.8)	11 (15.5)	11 (14.1)	13 (17.3)	8 (12.1)
2	25 (32.5)	16 (22.5)	22 (28.2)	24 (32.0)	18 (27.3)
3	19 (24.7)	32 (45.1)	26 (33.3)	24 (32.0)	26 (39.4)
4	8 (10.4)	5 (7.0)	7 (9.0)	11 (14.7)	7 (10.6)
5	9 (11.7)	3 (4.2)	8 (10.3)	2 (2.7)	4 (6.1)
6	0	1 (1.4)	0	1 (1.3)	0
Week 12					
0	4 (5.6)	3 (4.9)	3 (4.8)	1 (1.6)	0
1	15 (21.1)	9 (14.8)	14 (22.2)	11 (17.7)	9 (15.0)
2	27 (38.0)	24 (39.3)	15 (23.8)	17 (27.4)	14 (23.3)
3	17 (23.9)	20 (32.8)	17 (27.0)	24 (38.7)	24 (40.0)
4	4 (5.6)	3 (4.9)	12 (19.0)	8 (12.9)	10 (16.7)
5	4 (5.6)	2 (3.3)	2 (3.2)	1 (1.6)	3 (5.0)
6	0	0	0	0	0
Week 16					
0	10 (11.6)	5 (6.4)	3 (3.5)	1 (1.3)	3 (3.9)
1	15 (17.4)	13 (16.7)	16 (18.8)	15 (19.0)	11 (14.5)
2	23 (26.7)	27 (34.6)	15 (17.6)	27 (34.2)	20 (26.3)
3	24 (27.9)	27 (34.6)	36 (42.4)	27 (34.2)	33 (43.4)
4	7 (8.1)	5 (6.4)	13 (15.3)	7 (8.9)	5 (6.6)
5	5 (5.8)	1 (1.3)	2 (2.4)	2 (2.5)	4 (5.3)
6	2 (2.3)	0	0	0	0
Follow-up					
0	3 (3.8)	1 (1.6)	0	3 (4.4)	0
1	9 (11.3)	4 (6.3)	9 (13.0)	6 (8.8)	6 (9.0)
2	24 (30.0)	17 (27.0)	16 (23.2)	19 (27.9)	14 (20.9)
3	24 (30.0)	19 (30.2)	28 (40.6)	25 (36.8)	34 (50.7)
4	13 (16.3)	15 (23.8)	11 (15.9)	9 (13.2)	8 (11.9)
5	7 (8.8)	6 (9.5)	4 (5.8)	6 (8.8)	5 (7.5)
6	0	1 (1.6)	1 (1.4)	0	0

*Values are expressed as number (percentage); percentages may not equal 100 due to rounding. Percentages were calculated on the basis of the total number of patients with a Clinician's Global Impression score at each assessment. The scale is 0, very much improved; 1, much improved; 2, minimally improved; 3, no change; 4, minimally worse; 5, much worse; and 6, very much worse.

Figure 2. Difference in Response Rate Between Treatment Group and Placebo



The difference between galantamine and placebo response rate was, in all instances, less than the prespecified level for clinical significance (25%).

est mean decrease occurred in the 2.5-mg galantamine group. However, none of the observed changes were statistically significant.

Cognitive Function. Patients in this trial showed marked and significant slowing (all $P<.02$ or better) on all measures of response speed compared with an age-matched control group selected from the CDR normative database (simple reaction time: 329 ms vs 254 ms; choice reaction time: 490 ms vs 424 ms; digit vigilance speed: 441 ms vs 400 ms; articulatory working memory speed: 827 ms vs 695 ms; spatial working memory speed: 950 ms vs 897 ms; word recognition speed: 947 ms vs 815 ms; and picture recognition speed: 1014 ms vs 923 ms, respectively). While the ability to detect the targets in the digit vigilance task was also significantly impaired, the patients did not show impaired accuracy on the working and recognition memory tasks. To illustrate the magnitude of the impairments, the simple reaction time for patients with a mean age range of 37 to 39.1 years was 329 ms, which is longer than the simple reaction time of 308 ms from the normative database[32] for the highest age cohort of 80 to 87 years. All response measures were normally distributed.

Analysis of variance was conducted on the ITT LOCF group change from predosing data, terms being fitted for country, treatment, and the interaction between them. There were no significant main effects of treatment. However, the 3 measured effects observed between treatment and country (US vs Europe) reflected minor differences within active treatments between countries as opposed to differential placebo-active responding. There was no pattern for improvement for galantamine compared with placebo (Table 3). Changes in the placebo group were small (the 3 attention tasks showed a 1.5% overall improvement in speed, while the 4 memory tasks showed an overall improvement of 3.5% in the sensitivity indices), indicating that the placebo response did not account for the the absence of treatment effects.

Safety Evaluation. Of the 434 patients who were recruited, 304 completed the scheduled 16 weeks of treatment; 351 patients (80.9%) received galantamine hydrobromide; 389 patients (89.6%) reported adverse events, of which 88 (22.6%) of 389 patients withdrew. The rate of withdrawal due to adverse events in the placebo group was 15%. Overall, the number of adverse events increased with higher dosages of galantamine and fewer patients withdrew from the 2.5-mg galantamine group or from the placebo group compared with the groups receiving higher dosages. Although there was no statistical significance between the groups. Of the 130 patients who withdrew, 113 (86.9%) did so before the midpoint of the trial.

As expected from previous experience with galantamine, the most common adverse events reported by patients were nausea and headache, but these were also the most common adverse events reported by those taking placebo. Emergent depression was another adverse event, which led to 4 patient randomization breaks during the study. One patient committed suicide in the 10-mg galantamine group and 3 patients (one in the 2.5-mg galantamine group, one in the 7.5-mg galantamine group, and one in the placebo group) showed signs of depression with suicidal ideation. These 4 patients were included in the ITT analysis. There were 8 serious adverse events, but none was judged to be attributable to the drug (1 suicide, 1 nonfatal car crash, 4 surgical interventions, 1 lumbar disc prolapse, and 1 transient neurological disorder leading to hospitalization). The suicide was judged to be unrelated to the trial medication by an independent safety review panel and the coroner.

COMMENT

To our knowledge, this is the largest completed trial of CFS patients. Previous trials have been compromised by small sample size, poor randomization, retrospective analyses, short duration, and lack of standardized outcome measures.[35] This study failed to reveal galantamine as a clinically effective treatment for CFS and fibromyalgia.

Logistic regression analyses failed to identify any consistent factor predictive of outcome for any of the secondary efficacy measures including speed of onset (gradual, subacute, or acute), a preceding episode of viral illness (yes or no), duration of illness, type of clinic referral, or primary symptoms of CFS.

The lack of effect of galantamine on cognitive performance was surprising given the extent of the patients' cognitive impairment at baseline. The computerized cognitive assessment system used in this study has shown sensitivity to improvements with galantamine, particularly to attentional deficits in 4 previous trials in cohorts of Alzheimer patients.[28-30,33] Given the known benefits of anticholinesterases in Alzheimer disease, this suggests that the cognitive deficits seen in CFS are not due to cholinergic dysfunction.

The small reductions in cortisol levels seen in galantamine and placebo treatment groups across the 16-week trial were clinically insignificant, but may reflect reduction of stress secondary to the clinical attention that the patients were receiving.

Of potential interest for future studies of CFS is the nature and magnitude of the placebo response we observed. Sharpe et al[36] and Warren et al[37]

Table 3. Secondary Assessment End Points After 16 Weeks of Treatment

		Least Square Mean Change From Baseline				
			Galantamine Hydrobromide, mg, 3 times per day			
Assessment Scale	Range of Baseline Scores*	Placebo	2.5	5	7.5	10
Chalder Fatigue Rating Scale						
Physical	NA	9.86	9.25	8.77	11.02	9.99
Mental	NA	6.80	6.46	5.89	7.74	6.60
Fibromyalgia Impact Questionnaire						
Physical	12.57-14.36	−1.06	−2.64	−2.39	−1.29	0.06
Psychological	1.50-2.26	0.82	1.19	0.93	0.48	0.75
Social score	0.61-1.30	−0.03	0.01	0.05	0.01	0.09
Global well-being†	356-390	−53.89	−77.84	−88.65	−29.92	−60.67
Europe		−38.72	−75.68	−60.02	−4.33	−40.95
United States		−64.90	−54.61	−131.22	−63.15	−83.41
Nottingham Health Profile						
Part I	207.95-230.75	−45.67	−55.23	−79.56	−48.83	−57.43
Part II†	4.71-5.01					
Europe		−0.52	−0.79	−0.66	−0.37	−0.71
United States		−1.40	−1.00	−2.74	−0.37	−1.35
Pittsburgh Sleep Quality Index						
Total score	8.87-9.42	−2.02	−1.60	−2.28	−1.43	−1.73
Subjective sleep quality	1.64-1.73	−0.31	−0.24	−0.42	−0.18	−0.32
Sleep latency†	1.68-2.01					
Europe		−0.09	−0.31	−0.26	−0.31	−0.26
United States		−1.00	−0.39	−0.44	−0.33	−0.17
Sleep duration	0.68-0.90	−0.01	−0.02	−0.31	0.02	−0.13
Habitual sleep efficiency	1.04-1.16	−0.28	−0.09	−0.32	−0.09	−0.17
Sleep disturbance	1.57-1.69	−0.24	−0.11	−0.22	−0.18	−0.24
Use of medication	0.20-0.44	−0.20	−0.29	−0.16	−0.26	−0.17
Daytime dysfunction	1.73-1.86	−0.54	−0.48	−0.53	−0.34	−0.39
Plasma-free cortisol, µg/dL	3.77-55.35	−0.33	−1.69	−0.65	−0.23	−0.83
Computerized cognitive test‡						
Simple reaction time, ms	199-1083	−19.07	−4.09	4.45	0.18	−9.94
Choice reaction time, ms	302-1428	−19.84	−19.25	−1.73	−9.11	−17.70
Digit vigilance speed, ms	324-823	−2.90	−1.28	−3.95	4.47	7.46
Articulatory working memory sensitivity index	0.5-1.0	−0.001	0.008	0.02	0.01	0.03
Spatial working memory sensitivity index	0.1-1.0	−0.002	0.011	0.003	0.02	0.05
Delayed word recall, %	0-73.3	5.00	7.60	4.30	5.98	3.90
Word recognition sensitivity index	0.1-1.0	0.028	0.016	0.04	0.06	0.05
Picture recognition sensitivity index	0.2-1.0	0.012	0.022	−0.04	−0.02	−0.003

Abbreviations: CI, confidence interval; NA, not applicable.
*Represent the scores of each measured end point across all treatment groups at the premedication baseline visit.
†Comparisons between the United States and Europe were statistically significant.
‡Scores reflect improvement over predose performance.

state that placebo response rates in CFS are high, but (in contrast to placebo response rates in trials of psychiatric disorders) the present study obtained a rate of only 16.5%. We found that placebo response rates were higher in patients recruited from the United States, which may reflect recruitment biases.

Irrespective of treatment, the clinical improvement was consistently greater in patients treated in the United States compared with the European centers. This was not explicable on the basis of differences in severity or demographics, was independent of the treatment group, but it was observed most often in the 5-mg galantamine group and in the placebo group. There was no evidence of unblinding of the assessors involved, which could have introduced a bias in the various outcome measures.

Significant differences between patients in the United States and European centers were seen in some of the secondary end points with active treatment. However, the largest observed difference between US and European patients was seen in those taking placebo. The reasons for this are unclear but could include a greater willingness of CFS patients in the United States to report improvements.

An important finding of the present investigation was that the proportion of placebo responders (defined as CGI score of 0 or 1) increased steadily over the the trial (4 weeks, 10.5%; 8 weeks, 16.6%; 12 weeks, 15.0%; 16 weeks, 18.4%). After medication (galantamine or placebo) was withdrawn, the placebo response of 50% dropped sharply by week 4 follow-up to 9%. We believe that the improvement we observed across time (Figure 2) was due to nonspecific aspects of the trial setting. This has important implications for the interpretation of outcomes from various treatment programs for CFS patients who continue to improve while in contact with specialist services, but relapse when discharged back to primary care.

In conclusion, in this study, galantamine did not provide a significant clinical benefit in the treatment of patients with CFS.

Author Contributions: Dr Blacker had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
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Analysis and interpretation of data: Blacker, Greenwood, Wesnes, Howe, Ali.
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Funding/Support: This research was sponsored and funded by Shire Pharmaceutical Development Ltd, Andover, England.
Role of the Sponsor: Shire was responsible for the conduct of this study (protocol development, site selection, regulatory submissions, etc). A contract research organization was used in the United States for monitoring the sites and collection of data. All European involvement was managed by Shire. The clinical trial supplies were packaged and shipped by DHP Pharma (Crickhowell, Wales). The collection, monitoring, and data management of all primary and secondary end point data were in compliance with the provisions of good clinical practice. Data sets on the primary and all secondary end points were compiled by Shire's Biometrics Department and forwarded to the project statistician at Covance Maidenhead (Berkshire, England), which conducted the final statistical analyses in accord with an analysis plan reviewed by the Medicines Control Agency (subsequently renamed the MHRA) and by the US Food and Drug Administration.
Independent Statistical Analysis: Data sets for the interim analyses were forwarded by Shire's Biometrics Department to an independent statistician, Anne Whitehead, DSc, of the Medical and Pharmaceutical Statistics Research Unit, the University of Reading, Reading, England. Dr Whitehead undertook the interim analysis for and was a member of the independent data monitoring committee. Dr Whitehead had no involvement in the planning and conduct of the final analyses. However, she has verified that the results presented in this publication are consistent with her analyses and with the content of the Covance statistical report. Shire prepared the clinical trial report only.
Acknowledgment: We are indebted to Paul Levine, MD, George Washington University, Washington, DC, for his valuable advice and suggestions regarding patient recruitment and the conduct of the investigation in the United States.

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In science one tries to tell people, in such a way as to be understood by everyone, something that no one ever knew before. But in poetry, it's the exact opposite.
—Paul Dirac (1902-1984)