Galantamine — a Novel Cholinergic Drug with a Unique Dual Mode of Action for the Treatment of Patients with Alzheimer's Disease

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ABSTRACT

Galantamine hydrobromide is a tertiary alkaloid drug that has been developed and approved in a number of countries including the USA and several countries in Europe as a treatment for mild-to-moderate Alzheimer's disease (AD). Galantamine has a unique, dual mode of action. It is a reversible, competitive inhibitor of acetylcholinesterase (AChE), and is the only drug actively marketed for the treatment of AD with proven activity as an allosteric modulator of nicotinic acetylcholine receptors (nAChRs). This latter activity is thought to be particularly important since decreases in the expression and activity of nAChRs make a large contribution to the reduction in central cholinergic neurotransmission in patients with AD. Galantamine exhibits favorable pharmacokinetic characteristics including predictable linear elimination kinetics at the recommended maintenance doses (16 and 24 mg/day), a relatively short half-life (approximately 7 h) and high bioavailability. It is extensively metabolized in numerous pathways, mainly in the liver via cytochrome P450 enzymes CYP2D6 and CYP3A4, and has a low potential for clinically significant drug–drug interactions. During four large randomized, double-blind, placebo-controlled trials of up to 6 months duration, galantamine 16 and 24 mg/day significantly benefited cognitive and global function, ability to perform activities of daily living (ADL) and behavior, relative to placebo and baseline, for up to 6 months. Caregiver burden (time spent by caregivers supervising patients or assisting them with ADL), and caregiver distress (related to patients' behavioral symptoms) were also reduced. Cognitive and functional abilities were preserved at or near baseline for at least 12 months in patients who re-

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ceived galantamine 24 mg/day for 12 months in a long-term US study. These benefits were maximized by early and continued galantamine treatment and, again, were associated with significant reductions in caregiver burden. Trials of the efficacy of galantamine in dementia related to cerebrovascular disease have also yielded positive results. There are no safety concerns associated with the use of galantamine. The incidence of adverse events, particularly cholinergically mediated events affecting the gastrointestinal system, is generally low and can be minimized using the recommended slow dose-escalation scheme. Galantamine may, therefore, help to reduce the overall burden and cost involved in caring for dementia patients. Taking all evidence into account, galantamine has the potential to become a first-line therapy for dementia.

INTRODUCTION

Alzheimer's disease (AD) is the most common form of dementia, and estimates suggest that 15 million people worldwide have the condition (7). The first symptoms usually occur in patients over 60 years of age (52), and as the world's population ages, the resulting increase in the prevalence of the condition is becoming a major public health issue (7,21).

Traditionally, the objective of clinical trials of AD treatment has been symptomatic improvement of cognitive abilities. Using this as the main objective, in line with regulatory requirements, cholinesterase inhibitors have demonstrated the best evidence of efficacy in AD. However, assessments of other areas such as functional abilities and behavior, in addition to cognition, are needed to fully evaluate treatment effects (66). Recent AD treatment guidelines in the UK and USA (10,13) indicated possible doubts over the benefits of these drugs in functional abilities or behavior. Furthermore, in a progressive condition such as AD, postponing long-term decline in any of these areas may represent a more important benefit than transient short-term improvements (66). Published data from open-label extension studies of two currently available cholinesterase inhibitors, donepezil and rivastigmine, indicate that cognitive abilities, as assessed using the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog) fell below baseline after 38 and 40 weeks, respectively (15,46).

As a result of potential limitations of conventional cholinesterase inhibitors, the focus of drug development has shifted to agents with additional targets in the hope that drugs with novel mechanisms of action may have broader and more sustained efficacy.

Galantamine (Reminyl®) is a novel therapy that allosterically modulates nicotinic acetylcholine receptors (nAChRs) in addition to inhibiting acetylcholinesterase (AChE) (2). An extensive clinical trial program in patients with AD has shown that galantamine has broad, sustained benefits for at least 52 weeks in cognitive and functional abilities, global response and caregiver burden (42,44,54,55,63,64). In addition, galantamine delays the onset of behavioral symptoms (54). The benefits of galantamine were consistent across the different studies. AD treatment guidelines in the UK and USA agree that only galantamine has demonstrated benefits on cognitive, functional, global and behavioral outcomes (10,13).

The unique dual mode of action of galantamine may confer enhanced efficacy with the potential for additional therapeutic benefits in patients with AD. Long-term studies are still ongoing in AD, and the drug is also being evaluated in other forms of dementia that

Fig. 1. Chemical structure of galantamine.

may benefit from a combination of AChE inhibition and the modulation of nAChRs. Initial results in mixed and vascular dementia confirm the broad efficacy profile of galantamine (14).

This paper explains the mode of action of galantamine, and reviews the published clinical trial data to demonstrate the pharmacokinetics, safety and efficacy of this novel therapeutic option for AD.

CHEMISTRY

Galantamine, a tertiary alkaloid, has been isolated from the bulbs of the Caucasian snowdrops, *Galanthus woronowi* (41). It has also been isolated from the bulbs of the common snowdrop and several *Amaryllidaceae* plants (53). The chemical name of galantamine (Fig. 1) is (4a*S*, 6*R*, 8a*S*)-4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-6*H*-benzofuro[3a, 3, 2-*ef*][2]benzazepin-6-ol hydrobromide. Galantamine has three chiral centers; both the base compound and its hydrobromide salt are levorotatory. A synthetic version has since been produced.

PHARMACOLOGY

Galantamine has a unique dual mode of action, combining the reversible, competitive inhibition of AChE with positive allosteric modulation of nAChRs (2). It is the only drug actively marketed for the treatment of AD that has demonstrated both of these modes of action.

AChE Inhibition

In AD, decreased numbers of cholinergic neurons are correlated with cognitive deficits, such as reduced memory and learning (51). Reducing the breakdown of acetylcholine (ACh), a neurotransmitter produced in cholinergic neurons for release into the synaptic

Fig. 2. AChE inhibition, allosteric modulation and correction of the cholinergic deficit by galantamine.

cleft, by inhibiting the enzyme AChE, increases the availability of ACh in the synaptic cleft. This offsets the reduction in cholinergic function caused by degeneration of cholinergic neurons (Fig. 2).

Galantamine inhibits the breakdown of ACh by binding competitively and reversibly to the active site on AChE (2,56). Of particular importance are the inhibitory effects of galantamine on AChE in the frontal cortex and hippocampal regions of the brain — the two areas in which cholinergic neurotransmission is most affected in patients with AD (57).

Galantamine has a 53-fold greater inhibitory activity *in vitro* for AChE than for butyrylcholinesterase (BChE) (IC_{50} values were 0.35 and 18.6 $\mu\text{mol/L}$, respectively) (56,58,59). In healthy volunteers, median maximal Red Blood Cell AChE inhibition by galantamine is about 40% at thirty minutes after a single oral dose (10 mg) (5). AChE inhibition in AD patients given galantamine, 5 to 15 mg t.i.d. for 2 to 3 months, ranged from about 20 to 40% (56). This inhibition declined rapidly when galantamine treatment was stopped, and nearly no inhibition was seen at 30 h after the final dose (56).

The low affinity of galantamine for BChE may be responsible for a tolerability advantage. BChE, which is primarily found in plasma, is not thought to be directly involved in the cholinergic disruption seen in early AD, and its inhibition may contribute to peripheral adverse effects.

Modulation of nAChRs

Cholinergic neurons are subject to control via nAChRs (29), and reductions in the number of nAChRs in the brain play a pivotal role in the course of AD (37,40,51,62).

Several types of nAChR protein subunits are known. In the brain, there are nine known types of α -subunits (which bind ACh) and three types of β -subunits (the structural subunits). These subunits co-assemble in varying combinations to form a number of nAChR subtypes. In turn, the effects of pharmacological intervention on nAChRs vary. For instance, whereas α_7 nAChRs are sensitive to blockade by α -bungarotoxin, $\alpha_4\beta_2$ nAChRs (the most abundant subtype in the human brain) are not. However, both α_7 and $\alpha_4\beta_2$ nAChR subtypes are thought to be affected in AD brain (32,39,40).

Losses of nAChR subtypes are particularly noticeable in the hippocampus and neocortex, areas of the brain involved in memory and cognition (32,37–40). The importance of nAChRs is supported by findings that:

- Blockade of nAChRs leads to dose-related impairments in cognition (36)
- Nicotinic agonists transiently improve cognitive and psychomotor function in animals, healthy volunteers and patients with AD (23,31,48,65).

Galantamine binds to nAChRs at an allosteric (secondary) binding site on the α -subunit that is distinct from that at which ACh binds. Allosteric modulators, such as galantamine, are not capable of activating nAChRs on their own. However, when galantamine and ACh bind simultaneously to their respective binding sites on the same nAChR, galantamine augments the cellular response induced by ACh (2) (Fig. 2).

Galantamine makes nAChRs more sensitive to ACh, potentiating their response to available ACh. Moreover, electrophysiological experiments have consistently shown that, of the actively marketed drugs, galantamine is the only cholinergic treatment for AD that allosterically modulates nAChRs in this way (26,49). Measurements of ACh-induced whole-cell currents in single cloned human embryonic kidney (HEK293) cells expressing $\alpha_4\beta_2$ nAChRs demonstrate increases in response over a range of clinically relevant concentrations of galantamine (0.1–1.0 mol/L). Such increases are not observed with rivastigmine, donepezil, tacrine or metrifonate (49). The allosteric nature of the effect of galantamine on $\alpha_4\beta_2$ nAChRs has been confirmed by competitive inhibition experiments with the monoclonal antibody, FK-1, which binds specifically to the allosteric binding region of the α -subunit of nAChRs. Allosteric binding of galantamine to nAChRs (and hence, its effects on nAChR-mediated ion channel activity) is blocked in the presence of FK-1 (2,29).

In addition to the modulatory activity of galantamine on nAChRs, animal studies have suggested that the number of nAChRs increases during long-term treatment with the drug (4). However, the relevance of this activity is unknown. Other agents such as donepezil have also been shown to increase the number of nAChRs, although it is not known whether the “extra” receptors seen following treatment with either galantamine or donepezil are functional receptors, or whether these agents are able to bind to the new receptors (4).

In addition to mediating normal cholinergic neurotransmission, nAChRs may modulate the release of several other neurotransmitters, indicating that nAChRs may be involved in other brain functions such as the regulation of mood and psychological balance (51). Patients with AD may have lower than normal synaptic concentrations of other neurotransmitters, in addition to the widely recognized cholinergic deficit, that affects cognition, mood or behavior (28). For example:

- Reduced glutamate may exacerbate deficits in learning and memory
- Reduced serotonin (5-HT) may cause emotional disturbances (e.g., anxiety, depression)
- Reduced GABA may cause instability in behavior (e.g., sexual disinhibition, aggression).

The potential effects of galantamine on the release of these neurotransmitters may contribute to psychological and behavioral aspects of AD (28,61). The unique dual mode of action of galantamine may have important clinical benefits in addition to those seen with conventional agents that simply inhibit ACh degradation. Indeed, it is interesting to speculate from preliminary *in vitro* evidence that galantamine's effects on nAChRs may also affect other facets of the underlying disease pathology in AD. For instance, there is evidence showing that increased activity of nAChRs can protect against β -amyloid toxicity and reduced neurodegeneration, possibly due to increased release of the terminally truncated secreted form of amyloid precursor protein (11,24,25,69).

The allosteric modulatory activity of galantamine may also have a therapeutic advantage in terms of tolerability. Since galantamine by itself has low intrinsic potential to activate nAChRs, it would be expected to produce an optimal adjustment in nicotinic neurotransmission, avoiding overstimulation of nAChRs (27). This means that galantamine does not directly activate nAChRs and only potentiates submaximal ACh-induced responses. This mechanism alone would be expected to produce few, if any, side effects (28).

PHARMACOKINETICS

Absorption and Distribution

Galantamine has linear pharmacokinetics over the recommended daily dose range of 8 to 24 mg/day. Table 1 summarizes the pharmacokinetic properties of galantamine observed after a single oral dose (10 mg) in two Phase I studies involving healthy adult men (5,34). Galantamine is rapidly absorbed, time to reach peak plasma concentration is rapid, bioavailability is high, plasma protein binding is low (approximately 18%), and plasma half-life is short (approximately 7 h) (5,34).

Following repeated oral dosing of galantamine (12 and 16 mg b.i.d.), mean maximum plasma drug concentrations are 42 to 137 ng/mL and trough plasma concentrations vary from 29 to 97 ng/mL. No accumulation of galantamine was observed after 2 to 6 months

TABLE 1. Pharmacokinetic properties of galantamine after single oral doses (5,34)

Parameter	Measurements in healthy male volunteers
$C_{\max}$ ($\mu\text{g/L}$)	49–1150
$t_{\max}$ (h)	0.9–2.0
AUC ($\text{mg/L} \cdot \text{h}$)	4.77
F (%)	100
$T_{1/2}$ (h)	5.3–5.7
CL (L/h/kg)	0.3
V_{ss} (L/kg)	2.6

$C_{\max}$, maximum plasma drug concentration; $t_{\max}$, time taken to reach $C_{\max}$; AUC, area under the concentration–time curve; F , bioavailability; $T_{1/2}$, elimination half-life; CL, total plasma clearance; V_{ss} , volume of distribution at steady state.

of therapy (20). The volume of distribution of galantamine is large (mean value, 175 L), confirming its high degree of non-specific absorption (20).

Administration of galantamine with food delays the rate but not the extent of absorption of the drug in healthy volunteers (22). Following oral administration of single 10 mg tablets, peak plasma concentrations were reduced by approximately 25% and time to maximum concentration was more than doubled. Nevertheless, food had no effect on the total area under the concentration–time curve or elimination half-life (22).

Galantamine pharmacokinetics do not appear to be affected by mild hepatic impairment (Child-Pugh score, 5–6), and only modest increases (approximately 30%) in AUC and $T_{1/2}$ values were observed in subjects with moderate hepatic impairment (Child-Pugh score, 7–9) (67). A dose reduction by 8 mg/day should be considered in patients with moderate liver impairment. However, the use of galantamine is not recommended in patients with severe hepatic impairment.

Metabolism

Galantamine is primarily metabolized by cytochrome P450 (CYP) isoenzymes in the liver (20). Main metabolites include norgalantamine, *O*-desmethyl-galantamine, *O*-desmethyl-norgalantamine, epigalantamine and galantaminone (3,20). The AChE inhibitory activity of these metabolites *in vivo* is not believed to be clinically relevant as the amount of metabolism is fairly limited. No metabolites with notable AChE activity were detectable in an unconjugated form in plasma from either poor or extensive CYP 2D6 metabolizers. The AChE activity of galantamine is, therefore, almost exclusively due to unchanged galantamine.

Since galantamine is metabolized by CYP2D6 and CYP3A4, co-administration of galantamine with drugs that inhibit these isoenzymes could increase its cholinergic effects, with the potential to increase cholinergically mediated adverse events such as nausea and vomiting. For these reasons, a reduction of the galantamine maintenance dose can be considered during co-use of potent CYP2D6 inhibitors such as paroxetine, or CYP3A4 inhibitors such as ketoconazole and erythromycin (20).

Excretion

Renal clearance of galantamine in healthy volunteers after oral administration accounts for approximately 20–25% of total plasma clearance (5). Clearance of galantamine may be approximately 20% lower in women than in men. However, no clinically relevant differences in clearance have been observed in populations of different age, race or CYP2D6 metabolizer phenotypes (20,68).

The elimination of galantamine has been shown to be decreased in subjects with renal impairment (reduced creatinine clearance; < 9 mL/min), however peak and trough plasma concentrations were similar to those of patients with AD (20). A dose reduction of 8 mg/day should be considered in patients with moderate renal impairment. However, the use of galantamine is not recommended in patients with severe renal impairment.

CLINICAL STUDIES IN PATIENTS WITH AD

For medications to be effective in the long-term treatment of AD, they should have favorable, sustained effects on the global, cognitive, functional and behavioral symptoms of the illness. Using these criteria as a measure of treatment success, galantamine is a promising treatment. Here, data from four pivotal Phase III trials that demonstrated the safety and efficacy of galantamine in patients with mild-to-moderate AD are reviewed.

Pivotal AD Trials

All Phase III studies were randomized, double-blind, placebo-controlled, multicenter trials conducted in Australia, Canada, Europe, South Africa and/or the USA. Different doses and dose-escalation schemes were evaluated in order to ascertain the dose and escalation phase that provided optimal efficacy and tolerability.

- One international 3-month study compared placebo ($n = 125$) and galantamine 24 to 32 mg/day ($n = 261$) (44).
- One 5-month US study compared placebo ($n = 286$), galantamine 8 mg/day ($n = 140$), galantamine 16 mg/day ($n = 279$) and galantamine 24 mg/day ($n = 273$) (54).
- Two 6-month studies: one in the USA compared placebo ($n = 213$), galantamine 24 mg/day ($n = 212$) and galantamine 32 mg/day ($n = 211$) (42); one international study with placebo ($n = 215$) and galantamine 24 mg/day ($n = 220$) or 32 mg/day ($n = 218$) (64).
- At the end of the 6-month US study, patients who still met the inclusion criteria were eligible to enter a 6-month extension study (total study duration 12 months) using galantamine at 24 mg (42). Similar open-label extension studies were commenced on completion of other double-blind trials. However, final data analyses of other extension studies with galantamine are not yet available.

Patients met the National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's disease and Related disorders Association (NINCDS-ADRDA) criteria for probable AD (33). Upon study entry, patients had mild-to-moderate AD.

Outcome Measures

Cognition was assessed using the cognitive subscale of the ADAS-cog (47). In addition to its extensive use and applicability, the ADAS-cog is more sensitive to a wide range of disease severity and has specificity to major AD-related dysfunctions. Activities of daily living (ADL) were assessed using two instruments developed specifically for patients with AD: the Disability Assessment for Dementia (DAD) scale (19) and the Alzheimer's Disease Cooperative Study/Activities of Daily Living (ADCS/ADL) inventory (18). Both instruments assess items related to both basic self-care and instrumental ADL.

Behavioral symptoms were assessed by the Neuropsychiatric Inventory (NPI). This is a validated and reliable scale that was developed specifically to assess psychopathology in dementia patients (12).

In addition to assessing the severity and frequency of each symptom, the NPI also assesses the amount of caregiver distress engendered by each of the symptoms. This provided qualitative insight into the effects of galantamine on caregiver burden. Another

useful, quantitative indicator of overall burden is caregiver time, and this was assessed using a caregiver time questionnaire, the Activity of Caregiver Time Survey (ACTS) (6). ACTS was designed specifically to assess the amount of time spent supervising and assisting patients with ADL.

One of these pivotal trials also assessed the effects of galantamine on sleep quality, using the Pittsburgh Sleep Quality Index (PSQI) (9). Sleep quality is particularly important in AD since patients frequently display disturbed sleep patterns and this can impact on caregiver burden.

Overall response to treatment was measured with the Clinician's Interview-Based Impression of Change plus caregiver input (CIBIC-plus) (50).

All adverse events were recorded. Laboratory tests comprised biochemistry and hematology tests and urinalysis. Vital signs were assessed and physical examinations were performed to ascertain the patient's general condition at each visit. Resting 12-lead electrocardiograms (ECGs) were also performed and any clinically relevant changes occurring during the trial were recorded as adverse events.

Benefits of Galantamine on Cognition

In all 3 to 6 month Phase III studies, galantamine produced significant benefits on cognitive function relative to placebo (42,44,54,64). Galantamine maintained ADAS-cog scores above baseline levels in contrast with significant cognitive decline seen in placebo-treated patients. There was a mean drug-placebo difference of 3 to 4 points on ADAS-cog at the end of both 6-month studies (42,64). Furthermore, responder analyses showed that significantly more galantamine-treated patients than placebo-treated patients showed cognitive improvements that were pre-defined as a "treatment response" (e.g., improvements of ≥ 0 , ≥ 4 , or ≥ 7 points on the ADAS-cog) during clinical trials (42,54,64). Baseline disease severity, apolipoprotein-E4 genotype, age and gender did not affect the beneficial effects of galantamine on cognitive abilities.

Approximately 80% of patients who completed the 6-month US study entered the 6-month open-extension phase ($n = 353$), during which they received galantamine at 24 mg/day (42). Patients who received galantamine (24 mg/day) for the full 12 months (i.e. in the double-blind and open phases) had preserved cognitive function (Fig. 3) at the end of the study. This is very important, considering that the expected yearly decline in untreated patients with mild-to-moderate AD is 4 to 6 points on the ADAS-cog (1,35,60). Furthermore, patients who received galantamine 24 mg/day throughout the trial had better cognitive function than those who received placebo for the first 6 months ($p = 0.03$). This meant that the latter patients failed to "catch up", suggesting that early treatment with galantamine optimizes long-term outcome (Fig. 3).

Benefits of Galantamine on ADL

Galantamine maintained DAD or ADCS/ADL scores above baseline levels. The benefits of galantamine on ADL were observed for both instrumental (e.g., leisure, housework, finance and correspondence) and basic self-care (e.g., personal care, dressing and eating) activities.

In the 3-month study, galantamine produced significant benefits on ADL, as indicated by a drug placebo difference in the mean change from baseline DAD score of 4.3 points

Fig. 3. Galantamine maintains cognitive abilities for at least 12 months (42,60). Adapted, with permission, from: Winblad B. Maintaining functional and behavioral abilities in Alzheimer's disease. *Alzheimer Dis Assoc Disord* 2001;15(Suppl 1):S34-S41.

($p = 0.004$), and functional performance was preserved at baseline levels in galantamine-treated patients (44). In the 5-month US study, the drug-placebo difference in the mean change from baseline ADCS/ADL score was 2.4 to 3.5 points ($p < 0.01$, for both 16 and 24 mg vs. placebo) (54). At the end of this study, ADLs were preserved in galantamine-treated patients, whereas the placebo group experienced significant decline ($p < 0.05$). These findings were supported by the results of the 6-month international study, in which DAD scores were improved in the galantamine group at 6 months, compared with placebo (64).

In the 6-month US study, there were no significant differences in DAD scores between galantamine and placebo at 6 months (42). However, at the end of the 6-month extension phase, patients who received galantamine (24 mg/day) for 12 months maintained functional abilities, while patients who received placebo for the first 6 months experienced significant decline ($p < 0.001$ vs. baseline) (Fig. 4) (42). In comparison, after 12 months, untreated patients would be expected to deteriorate by 11 to 13 points on the DAD scale (17,60). The effect of galantamine in maintaining DAD scores at baseline levels provides important benefits in stabilizing patients with AD.

Benefits of Galantamine on Behavior

Galantamine postponed the emergence of behavioral symptoms. At the end of the 5-month study, galantamine at 16 and 24 mg/day produced significant benefits on behavioral symptoms, as indicated by a drug-placebo difference in mean change from baseline NPI score of 2.4 points ($p < 0.05$ for both doses vs. placebo) (Fig. 5) (54). The NPI scores for the 16- and 24-mg/day galantamine groups were not significantly different from baseline values, whereas the placebo group experienced a significant decline ($p < 0.05$ vs. baseline).

Fig. 4. Galantamine maintains functional abilities. Adapted, with permission, from: Winblad B. Maintaining functional and behavioral abilities in Alzheimer's disease. *Alzheimer Dis Assoc Disord* 2001;15(Suppl 1): S34–S41.

Fig. 5. Galantamine postpones the emergence of behavioral symptoms (54). Adapted, with permission, from: Tariot P et al. A 5-month, randomised, placebo-controlled trial of galantamine in AD. *Neurology* 2000;54: 2269–2276.

Of the 10 behavioral items comprising the NPI, galantamine showed most marked benefits on symptoms of aberrant motor behavior, anxiety, disinhibition and hallucinations.

Benefits of Galantamine on Global Response

The benefits of galantamine on cognitive and functional abilities and behavioral symptoms were reflected in assessments of global response in the four pivotal Phase III trials. The significant benefits in global function also demonstrated the clinical relevance of galantamine's effects on individual aspects of the disease.

In all studies, CIBIC-plus scores were significantly better in patients treated with galantamine compared with those receiving placebo (all $p < 0.05$). More patients treated with galantamine at 16, 24, or 32 mg/day, compared with those who received placebo, remained stable or improved on the CIBIC-plus over 3, 5, or 6 months (42, 44,54,64).

Benefits of Galantamine on Sleep Quality

In the 3-month, international study, no significant differences in sleep quality, as assessed using the PSQI, were observed between patients treated with galantamine and those receiving placebo (45).

Adverse effects on sleep have been noted in patients receiving conventional AChE inhibitors (8,46). In a study assessing the efficacy and tolerability of galantamine in patients switched from previous donepezil treatment, PSQI scores were significantly improved within 6 weeks of commencing galantamine therapy (43).

The broad, sustained efficacy of galantamine does not appear to be at the expense of drug-induced sleep disturbance (43,45). The absence of sleep disturbance, together with all of the other benefits associated with galantamine, would be expected to improve the quality of life of patients and caregivers. Furthermore, patients who suffer from sleep disturbance while on donepezil may benefit from switching to galantamine (43).

Benefits of Galantamine on Caregiver Burden

The broad benefits of galantamine, as described above, lead to long-term reduction and stabilization of caregiver time and/or distress.

The effects of galantamine (24 or 32 mg/day) on caregiver time were evaluated in the 6-month international study. After 6 months, time spent assisting patients with ADL each day had decreased by 15 to 38 min in the galantamine group, but increased by 23 min in the placebo group ($p < 0.05$). Time spent supervising patients was maintained at baseline levels in the galantamine group, but increased by about 2 h in the placebo group ($p < 0.001$ vs. baseline) (Fig. 6) (63).

At the end of the 5-month US study, distress in the caregivers of the placebo group (as assessed using the NPI distress scale) was significantly increased over baseline. In both the galantamine 16- and 24-mg/day groups, caregiver distress scores were not significantly different from baseline at the end of the study (Fig. 7). This reduction in caregiver distress reflects the effects of galantamine in delaying the emergence of behavioral symptoms in patients with mild-to-moderate AD (55).

Caregiver burden is strongly correlated with the decision to institutionalize a patient. Through its effects on caregiver burden, galantamine may help patients remain at home for longer, improving their quality of life and reducing costs to society.

Safety and Tolerability of Galantamine

Galantamine is not associated with any major safety concerns. During the Phase III clinical trial program, galantamine demonstrated good tolerability with no clinically relevant effects on vital signs or laboratory changes. There was a high completion rate in all pivotal studies, even though nearly all patients had comorbidities (98%) or were receiving concomitant medications (96%). The frequency of adverse events was low across the

Fig. 6. Galantamine reduces the time caregivers spend supervising patients. Adapted, with permission, from: Blesa R. *Dement Geriatr Cogn Disord* 2000;11(Suppl 2):28–34.

Fig. 7. Galantamine reduces caregiver distress.

Phase III program, and most events were mild in severity. Most adverse events, including nausea and vomiting, occurred during dose-escalation phases. However, these adverse events were transient and generally resolved with continued treatment without dose modification.

The recommended optimal dosing regimen was found to consist of a 4-week dose-escalation scheme, whereby patients receive 8 mg/day for 4 weeks, followed by an initial

TABLE 2. Adverse events occurring in $\geq 5\%$ of patients more often with galantamine than with placebo when using a 4-week dose-escalation scheme (54)

	Placebo (%) (n = 286)	Galantamine (%)	
		16 mg/day (n = 279)	24 mg/day (n = 273)
Any adverse event	72	73.8	80.2
Nausea	4.5	13.3	16.5
Vomiting	1.4	6.1	9.9
Anorexia	3.1	6.5	8.8
Diarrhea	5.9	12.2	5.5

Adapted, with permission, from: Tariot P et al. A 5-month, randomised, placebo-controlled trial of galantamine in AD. *Neurology* 2000;54:2269–2276.

maintenance dose of 16 mg/day. After at least another 4 weeks, the dose may be increased to 24 mg/day, if and when the physician believes that such a dose increase will provide benefits to the individual patient. When this dosing regimen was used in the 5-month pivotal study (54), discontinuation rates due to adverse events were low in patients treated with galantamine at 16 and 24 mg/day (7 and 10%, respectively), and were comparable with those seen in placebo-treated patients (7%). The incidence of cholinergically mediated adverse events (particularly those involving the gastrointestinal system) was low in this study (54). Table 2 lists adverse events occurring in at least 5% of patients in the 5-month US study, which used the 4-week dose-escalation scheme.

The safety and tolerability profile of galantamine remained favorable during extended periods of treatment, as seen from results of the 6-month open-label extension of the 6-month US study (42). The overall incidence of adverse events during the extension phase was 85.3% compared with 78.9% during double-blind treatment. No unexpected, time-dependent adverse events occurred during the extension phase. Minimal weight loss was observed during long-term galantamine treatment. Although some reduction in mean body weight did occur during a 6-month double-blind treatment ($p < 0.001$), patients appeared to recover this during the extension phase, and the mean weight loss at Month 12 was just 1.5 kg (42).

GALANTAMINE AND OTHER DEMENTIA TYPES

Regardless of the underlying etiology of dementia, cognitive impairment is associated, in most cases, with deficits in central cholinergic neurotransmission. This cholinergic deficit can be accounted for by alterations in nAChR expression in the brain. For example, the central cholinergic system is impaired in many patients with vascular dementia, and the reduction in numbers of nAChRs is at least as extensive in Parkinson's disease or dementia with Lewy bodies as it is for AD (30). Furthermore, while cholinergic deficit is the main contributor to clinical cognitive dementia symptoms, other neurotransmitters may be affected in different regions of the brain in different types of dementia. Galantamine's unique dual mode of action, and its potential modulatory effects on other neurotrans-

mitters (e.g., glutamate, GABA, serotonin), may provide beneficial effects on a range of dementia types.

A recently completed study investigated the effects of galantamine in patients with a clinical diagnosis of probable vascular dementia or mixed dementia (AD combined with cerebrovascular disease) (14). Patients diagnosed with probable vascular or mixed dementia received galantamine at 24 mg/day ($n = 396$) or placebo ($n = 196$) for 6 months. Galantamine showed statistically significant therapeutic effects on all key areas of cognitive and non-cognitive abilities (function, behavior and global response). Galantamine was well-tolerated. This is the first randomized, controlled trial of a cholinergic drug in patients with probable vascular or mixed dementia, and the fact that galantamine demonstrated such broad benefits is extremely encouraging. The future holds promise of effective treatment not only for patients with AD, but also those with co-existing cerebrovascular disease and those with vascular dementia.

Further trials are currently underway in a range of other conditions to determine whether the sustained, broad spectrum of efficacy that galantamine shows in AD extends to patients with other types of dementia. These studies promise to reveal exciting data and potentially open new therapeutic opportunities for a range of patients for whom little therapeutic help has been available to date.

CONCLUSIONS

Galantamine is an effective and well-tolerated treatment for patients with AD. It provides consistent, broad, sustained, clinically relevant benefits in key areas of AD. The unique dual mode of action of galantamine could explain its impressive efficacy profile, and the potential for additional benefits with galantamine (over conventional cholinesterase inhibitors) has recently been recognized in recommendations arising from evidence-based medical assessments. The recent NICE Report and AAN Guidelines (10,13) indicate that galantamine has proven benefits in cognition, function, behavior and global response, while proven benefits of donepezil and rivastigmine may be more limited. In addition, galantamine maintains cognitive and functional abilities at baseline levels for at least a year (42). While Mini-Mental State Examination (MMSE) scores were seen to be maintained around baseline levels for up to 52 weeks in a secondary analysis in one placebo-controlled study with donepezil (66), no similar long-term (> 1 -year) changes on the ADAS-cog have been published with other cholinergic agents. The broad, sustained efficacy profile of galantamine in AD, not so far observed with conventional cholinesterase inhibitors, may reflect its unique dual mode of action.

Galantamine has a good tolerability profile, and there do not appear to be any serious safety concerns associated with its use. As with other cholinergic drugs, the most frequent adverse events with galantamine are gastrointestinal events such as nausea, vomiting and diarrhea. However, the incidence of these side effects can be minimized by using a 4-week dose-escalation schedule on initiation of therapy (54). This dose-escalation scheme, which is now recommended in the labeling for Reminyl® (galantamine) tablets, features a simple, single step to an initial maintenance dose of 16 mg/day. The recommended dosing scheme also allows added flexibility if an increase to a higher maintenance dose

(24 mg/day) is thought necessary, based on physicians' clinical judgement of individual response and tolerability. Importantly, the broad spectrum of benefits of galantamine in patients with AD does not appear to be at the expense of drug-induced sleep disturbance (43,45).

Galantamine is an effective treatment for Alzheimer's disease (AD) with an excellent tolerability profile. The availability of this novel drug is a significant addition to the armamentarium of drugs approved for the treatment of patients with AD. The future will show whether these benefits extend to patients with other types of dementia.

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