REVIEW ARTICLE

A comparison of donepezil and galantamine in the treatment of cognitive symptoms of Alzheimer's disease: a meta-analysis

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This review was conducted in order to determine the efficacy of donepezil and galantamine in the treatment of cognitive symptoms of Alzheimer's disease, and also to determine whether galantamine was a superior pharmacological intervention. Meta-analytic methods were used to analyse the data from eight empirical studies which met the inclusion criteria specified. By finding the mean effect sizes of the treatment on the outcome measures of cognition, it was determined that neither drug was greatly efficacious. However, this result does not necessarily diminish the practical value of the drug. It was also found that galantamine was no better than donepezil at treating cognitive decline in AD. Copyright © 2005 John Wiley & Sons, Ltd.

KEY WORDS — donepezil; galantamine; Alzheimer's; pharmacology; meta-analysis

INTRODUCTION

Alzheimer's disease (AD), also known sometimes as dementia of the Alzheimer's type, is the most prevalent cause of dementia in the aged population. It is a progressive neurodegenerative disorder which accounts for about 50% to 70% of dementia in older people. Although AD can only be conclusively diagnosed at autopsy, the evolution of new techniques for structural and functional imaging of the brain has allowed more insight into the epidemiology of the disease. Diagnosis has also been improved by the provision of more defined guidelines to diagnosing AD by the National Institute of Neurologic and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS—ADRDA) in 1984 (Ishii *et al.*, 1991).

Age is the primary risk factor of AD. Gender is also a risk factor; women are more likely to die from AD than men. Other risk factors include a history of head injury and the presence of the apolipoprotein e4 allele (Davidson *et al.*, 2002). Several rare, causative genetic mutations have been identified in AD, including the mutation of the amyloid precursor protein on chromosome 21, and presenilin genes 1 and 2 on chromosomes 14 and 1, respectively (Cummings, 2003).

The most prominent neurobehavioural deficit of AD is memory impairment (Banich, 1997; Cummings, 2003). Patients with AD also suffer visuospatial difficulties, executive function impairment and language difficulties. The pathophysiology of AD includes amyloid plaques and neurofibrillary tangles, both of which cause atrophy of the cortex (Banich, 1997; Cummings, 2003). There is also atrophy in the nucleus basalis, which causes the cholinergic deficit observed in patients with AD (Cummings, 2003).

The loss of cholinergic transmission is believed to be the cause of the deterioration of cognitive function seen in patients with AD (Francis *et al.*, 1999). This hypothesis, known as the cholinergic hypothesis, spawned the use of pharmacological interventions that increase the activity of the system, and so retard the progression of cognitive impairment. This was most successfully done with acetylcholinesterase inhibitors. These drugs inhibit the activity of acetylcholinesterase in the synaptic cleft, hence increasing the

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amount of acetylcholine available for neurotransmission, enhancing the activity of the cholinergic system. Two of these drugs, donepezil (Aricept[®]) and galantamine (Reminyl[®]), are the focus of this review.

Donepezil was approved for treatment of mild-to-moderate AD in the USA in 1996. In 1997, it was approved in the UK, and in Canada as the first drug treatment for AD. It is highly selective for acetylcholinesterase, has few side-effects, and in the literature, is said to have beneficial effects on cognition and daily living in AD patients (Jones, 2000). Galantamine has also shown similar results. It was approved for treatment of mild-to-moderate AD in the USA and Canada in 2001. However, galantamine has a modus operandi somewhat different to that of donepezil: in addition to inhibiting acetylcholinesterase, galantamine also allosterically modulates the nicotinic receptors in the cholinergic system. This action increases the release of acetylcholine, and so enhances cholinergic activity (Maelicke, 2000).

This difference in drug mechanisms begs the question: which drug is more effective? Does galantamine's dual mechanism make it a superior intervention to donepezil in the treatment of AD? This review aims to determine the efficacy of donepezil and galantamine in the treatment of the cognitive deficits of AD, and determine which drug is the superior pharmacological intervention.

METHOD

The method used to carry out this investigation was meta-analysis. Meta-analytic techniques provide a means of quantifying the magnitude of an effect or a deficit. The magnitude of the effect was indexed in this study by the effect size statistic, Cohen's d, which is a measure of the degree to which a phenomenon is present, or in theoretical terms, the degree by which the null hypothesis is false (Zakzanis, 1998). The meta-analysis reports the mean effect size, which reflects the average of all the effect sizes of the studies included in the review. The mean effect size is then interpreted in terms of the study.

Cohen's d can be converted to a corresponding overlap statistic (OL%), which directly shows the percentage of overlap between patient and control samples. Also, Cohen's benchmarks provide a useful guide to interpreting the effect size. Cohen assigned the labels of a small effect to a d of 0.2, a medium effect to a d of 0.5, and a large effect to a d of 0.8 (Zakzanis, 2001). While this is a useful frame of reference, it is not always practical, and care should be taken to interpret the importance (not to be confused with statistical significance) of the effect size in the context of the study.

Meta-analyses control for biases that are potentially present in significance testing, such as subjective study selection and inaccurate interpretations of statistical findings (Wolf, 1986). Also, Cohen's d does not necessitate the assumption of homogeneity of variance, as it controls for participant variability. Meta-analyses also account for the 'file-drawer' problem by reporting the fail-safe N statistic. This statistic tells the number of studies needed to overturn the mean effect size that was obtained in the meta-analysis (Zakzanis, 2001). This statistic can be a good indication as to whether or not the results of the study can be generalized.

Literature search

The review of the available literature began with a search on Psyc-Info and PubMed. Using the advanced search option, the search was done through the database using key words as follows: galantamine, galanthamine, Reminyl, donepezil, Aricept, Alzheimer, dementia, efficacy, pharmacology. Relevant articles were found in eight journals, both through the electronic databases and through manual searches. The articles were retrieved through online access to the journals, and from Gerstein Science Information Centre at the University of Toronto.

Study inclusion criteria

Criteria for articles to be included in this study are outlined in Table 1. Publication after 1984 ensures that all participants were diagnosed according to the NINCDS—ADRDA criteria. The randomized, double-blind design reduced the risk of researcher biases in the reporting and interpretation of the results. Effect sizes were computed from statistics such as means, standard deviations and standard errors of the mean.

Recorded variables

Recorded variables in the studies included in this investigation were mean age, gender, weight and ethnicity. The scores on the screening MMSE were also

Table 1. Study inclusion criteria

(a) Publication after 1984
(b) A randomized, double-blind, placebo controlled study design
(c) Participants with mild to moderate AD, and without current diagnosis of any other psychiatric or neurological disorder
(d) Outcome measures of cognitive ability in AD patients
(e) Study statistics convertible to the effect size statistic d

Table 2. Characteristics and participant demographics of donepezil studies

Study (Authors and publication year)	Duration (weeks)	Number of participants	Male (%)	Mean age (years)	Outcome measure(s)	Dosages (mg/day)
Rogers *et al.* (1998b)	24	455	38	73.4	ADAS-cog, MMSE	5, 10
Rogers *et al.* (1998a)	12	394	37	73.7	ADAS-cog, MMSE	5, 10
Homma *et al.* (2000)	24	205	33	69.8	ADAS-Jcog	5

Table 3. Characteristics and participant demographics of galantamine studies

Study (Authors and publication year)	Duration (months)	Number of participants	Male (%)	Mean age (years)	Dosages (mg/day)
Tariot *et al.* (2000)	5	775	36	76.8	8, 16, 24
Wilcock *et al.* (2000)	6	653	37	72.5	24, 32
Raskind *et al.* (2000)	6	405	38	75.4	24, 32
Rockwood *et al.* (2001)	3	278	44	74.9	24, 32
Wilkinson *et al.* (2001)	3	188	42	73.8	18, 24, 36

recorded. Outcome measures of cognition were the Alzheimer's disease assessment scale-cognitive (ADAS-cog), the Japanese version of the ADAS-cog, and the mini-mental state examination (MMSE).

RESULTS

Eight studies met the inclusion criteria for this investigation; three on donepezil, and five on galantamine. In total, test results from 1174 AD patients treated with placebo, 668 treated with donepezil, and 1510 treated with galantamine were recorded across meta-analyses.

Table 2 includes a description of the study characteristics and demographics of the participants in the studies on donepezil. The age of the participants did not vary significantly across the studies. Notably, all three studies had approximately twice the number of female participants than male participants. Two of the studies used the MMSE as well as the ADAS-cog as outcome measures of cognition, and Homma *et al.* (2000) used the ADAS-Jcog.

Table 3 includes a description of the characteristics and the demographics of the galantamine studies. All

of these studies used the ADAS-cog as a measure of cognition. As with the donepezil studies, there were considerably more female participants than male participants.

Table 4 includes the mean effect sizes for the measures of cognition across all the studies. Effect sizes were computed according to Cohen's *d* formula where the mean change of the treatment group was subtracted from the mean change of the placebo group, calibrated in pooled standard deviation units (Zakzanis, 2001). This table also includes the number of effect sizes which contributed to each mean. Effect sizes were computed for each treatment dosage of the drug. Also included in the table are the standard deviation of the mean effect size, the overlap percentage (OL %), and the minimum and maximum effect sizes that contributed to the mean. The fail-safe *N* at a criterion of 0.02 was also calculated for each outcome measure.

The ADAS-cog evaluation of donepezil yielded a *d* of 0.48, which translates to an overlap percentage of 67.8. The MMSE yielded a *d* of −0.36, which yielded an overlap percentage of 75.6. It should be noted that the ADAS-cog yields a positive *d*. This reflects the

Table 4. Meta-analytic results across studies

Drug and outcome measure	*N*	Mean *d*	(SD)	OL%	Min. *d*	Max. *d*	Fail-safe *n*
Donepezil							
ADAS-cog/Jcog	5	0.48	2.25	67.8	0.40	0.57	7
MMSE	4	−0.36	0.03	75.6	−0.38	−0.32	4
Galantamine							
ADAS-cog	12	0.52	0.10	65.6	0.27	0.68	20

placebo group having a higher score; a higher score on the ADAS-cog means greater dysfunction. The negative d on the MMSE means that the placebo did worse on the test than the treatment group; lower scores mean greater dysfunction. Galantamine showed a d of 0.52 on the ADAS-cog, which means an overlap percentage of 65.6.

DISCUSSION

This review was conducted on the clinical trials of the drugs donepezil and galantamine to determine and compare their respective efficacies in treating the cognitive symptoms of AD. Using meta-analytic techniques on the available literature, it was possible to determine how effective each of the drugs was.

While some of the AD patients treated with donepezil showed better cognitive function than the participants in the placebo group, the number was far from the majority. As evident from the mean effect size, most patients showed the same decline in cognitive function as did the placebo-treated patients. Galantamine showed the same result. The majority of people treated with galantamine in those studies showed the same cognitive deficits on the scales as did the patients in the placebo groups.

This brings to question the practicality of the use of either donepezil or galantamine as interventions of the cognitive decline that befalls AD patients. The mean effect sizes of donepezil and galantamine on the ADAS-cog were 0.48 and 0.52, respectively. If interpreted according to Cohen's benchmarks, these effect sizes would fall just along the border of low to moderate efficacy of the drug. That does not paint a promising picture for patients with AD.

However, it is not entirely sensible to draw all conclusions about the practicality of the pharmacological interventions based solely on their small effect. AD is a progressive neurodegenerative disorder, which is always terminal, and is still incurable. The effect that donepezil and galantamine have may be small, but it exists nonetheless. Anything that could possibly slow the progression of AD, and give the patients a bit more time, should be welcomed.

Perhaps a better analysis of the practicality of these drugs would be a consideration of their cognitive enhancements in conjunction with their effects on the functional disability of patients with AD. It stands to reason that an improvement in cognitive function would also mean an improvement in the functional performance of AD patients. Also, the level of functional performance also contributes heavily to the quality of life that a person with AD experiences

(Wolfson *et al*., 2000). A meta-analysis of the effects of donepezil and galantamine on the functional performance and quality of life of AD patients may serve to give a better idea of the efficacy of the drugs, and their usefulness in treating AD.

The second purpose of this review was to compare the efficacy of donepezil with that of galantamine. Galantamine does not seem to have an advantage. This seems counter-intuitive, because galantamine's mechanisms, theoretically, are designed to increase the amount of acetylcholinesterase in the synaptic cleft to a greater extent than donepezil. Donepezil only inhibits acetylcholinesterase. Galantamine inhibits acetylcholinesterase, modulates presynaptic nicotinic receptors so that they release more acetylcholine, and modulates postsynaptic nicotinic receptors so that the neuron is activated. Despite this, it does not seem to be more effective than donepezil. This could be because donepezil may just be a more powerful drug, despite the relative simplicity of its action. Perhaps donepezil inhibits acetylcholinesterase more than galantamine.

An alternative explanation is that the modulation of nicotinic receptors does not help the cholinergic system as much as would be believed. Allosteric modulation of the presynaptic nicotinic receptors is capable of increasing the amount of glutamate, as well as acetylcholine, released into the synaptic cleft (Maelicke, 2000). However, increased levels of glutamate in the central nervous system have also been associated with neuronal dysfunction and cell death (Danysz and Parsons, 2003). By allosterically modulating the nicotinic receptors, galantamine may be causing harm as well as good.

This investigation is not without its limitations. The number of effect sizes contributing to the mean is small, and therefore these results cannot be generalized. As seen by the small fail-safe N, these results can be overturned easily with a minimal number of studies with negligible effect sizes. Another limitation is the possibility of moderator variables that this study did not account for. For example, the doses of the acetylcholinesterase inhibitor used, as well as the duration of the study, may have had a significant impact on the effect sizes obtained. Correlational analyses would have to be done to understand exactly how these moderator variables may have affected the outcome of this study.

CONCLUSIONS

This meta-analytic review aimed to discover the efficacy of two of the acetylcholinesterase inhibitors used to reduce the rate of decline in patients with AD,

namely donepezil and galantamine. By evaluation of the mean effect size across a number of studies, it was found that neither drug was greatly efficacious. However, this does not mean they are worthless, for any treatment for a progressive incurable disorder has practical value.

It was also found that galantamine does not have an advantage over donepezil, despite its dual mechanisms of increasing cholinergic activity. This could be because the drug simply has inferior pharmacokinetics to donepezil. It could also be because galantamine may be cancelling out the good that it does by harming the cholinergic system with increased levels of glutamate. Further studies on the neurotransmission of patients on galantamine are needed to rule out this hypothesis.

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