ORIGINAL ARTICLE

Cost-Effectiveness: Cholinesterase Inhibitors and Memantine in Vascular Dementia

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ABSTRACT: ***Background:*** Several randomized controlled trials of cholinesterase inhibitors and memantine in mild to moderate vascular dementia have demonstrated the efficacy of these treatments. However, given these drugs incur considerable cost, the economic argument for their use is less clear. ***Objective:*** To determine the incremental cost-effectiveness of cholinesterase inhibitors and memantine for mild to moderate vascular dementia. ***Design:*** A decision analysis model using a 24-28 week time horizon was developed. Outcomes of cholinesterase inhibitors and memantine and probabilities of adverse events were extracted from a systematic review. Costs of adverse events, medications, and physician visits were obtained from local estimates. Robustness was tested with probabilistic sensitivity analysis using a Monte Carlo simulation. ***Interventions:*** Donepezil 5 mg daily, donepezil 10 mg daily, galantamine 16-24 mg daily, rivastigmine flexible dosing up to 6 mg twice daily, or memantine 10 mg twice daily versus standard care. ***Main Outcome Measures:*** Incremental cost-effectiveness ratio (ICER) expressed as cost per unit decrease in the Alzheimer's Disease Assessment Scale-cognitive (ADAS-cog) subscale. ***Results:*** Donepezil 10 mg daily was found to be the most cost-effective treatment with an ICER of $400.64 (95%CI, $281.10-$596.35) per unit decline in the ADAS-cog subscale. All other treatments were dominated by donepezil 10 mg, that is, more costly and less effective. ***Conclusion:*** From a societal perspective, treatment with cholinesterase inhibitors or memantine was more effective but also more costly than standard care for mild to moderate vascular dementia. The donepezil 10 mg strategy was the most cost-effective and also dominated the other alternatives.

RÉSUMÉ: Rapport coût-efficacité des inhibiteurs de la cholinestérase et de la mémantine dans la démence vasculaire. ***Contexte :*** Plusieurs études contrôlées et randomisées portant sur des inhibiteurs de la cholinestérase et sur la mémantine, chez des patients présentant une démence vasculaire de légère à modérée, ont démontré l'efficacité de ces médicaments. Cependant, étant donné leur coût élevé, les répercussions économiques de leur utilisation sont mal connues. ***Objectif :*** Le but de l'étude était de déterminer l'accroissement du rapport coût-efficacité (ARCE) dû à l'utilisation des inhibiteurs de la cholinestérase et de la mémantine dans la démence vasculaire de légère à modérée. ***Plan d'étude :*** Nous avons développé un modèle d'analyse de décision portant sur une durée d'utilisation de ces médicaments de 24 à 28 semaines. Les résultats thérapeutiques obtenus avec les inhibiteurs de la cholinestérase et la mémantine et les probabilités d'incidents thérapeutiques ont été tirés d'une revue systématique. Les coûts des incidents thérapeutiques, de la médication et des visites chez le médecin proviennent d'estimés locaux. La robustesse a été testée par analyse de sensibilité probabiliste au moyen d'une simulation Monte Carlo. ***Interventions :*** Nous avons évalué l'administration quotidienne de 5 mg de donépézil, de 10 mg de donépézil, de 16 à 24 mg de galantamine, d'un dosage flexible de rivastigmine jusqu'à 6 mg deux fois par jour ou de mémantine 10 mg deux fois par jour par rapport au traitement conventionnel. ***Principales mesures des résultats :*** Nous avons déterminé l'ARCE, défini comme étant le coût de la diminution d'une unité du score au test de l'Alzheimer's Disease Assessment Scale-cognitive (ADAS-cog) subscale. ***Résultats :*** Nous avons constaté que l'administration de 10 mg de donépézil était le traitement qui présentait le meilleur rapport coût-efficacité, soit un ARCE de $400,64 (IC à 95% : $281,10 à $596.35) pour une baisse d'une unité à l'ADAS-cog. L'administration de 10 mg de donépézil était supérieure à tous les autres traitements : ils étaient tous plus coûteux et moins efficaces. ***Conclusion :*** D'un point de vue sociétal, le traitement par les inhibiteurs de la cholinestérase ou la mémantine était plus efficace mais également plus coûteux que le traitement conventionnel dans la démence vasculaire de légère à modérée. L'administration de 10 mg de donépézil constituait la stratégie dont le rapport coût-efficacité était le meilleur et était supérieure à toutes les autres alternatives.

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In 1991, the Canadian Study of Health and Aging estimated the annual net cost of dementia care in Canada exceeded $3.9 billion; the most significant component of the total cost was for care in long-term care institutions and assistance with activities of daily living by others.[1] By comparison, Health Canada estimated the total cost of cardiovascular diseases to be $18,472 million in a 1998 report.[2]

Based on the Canadian Study of Health and Aging data, the prevalence of vascular dementia increases from 0.6% in those

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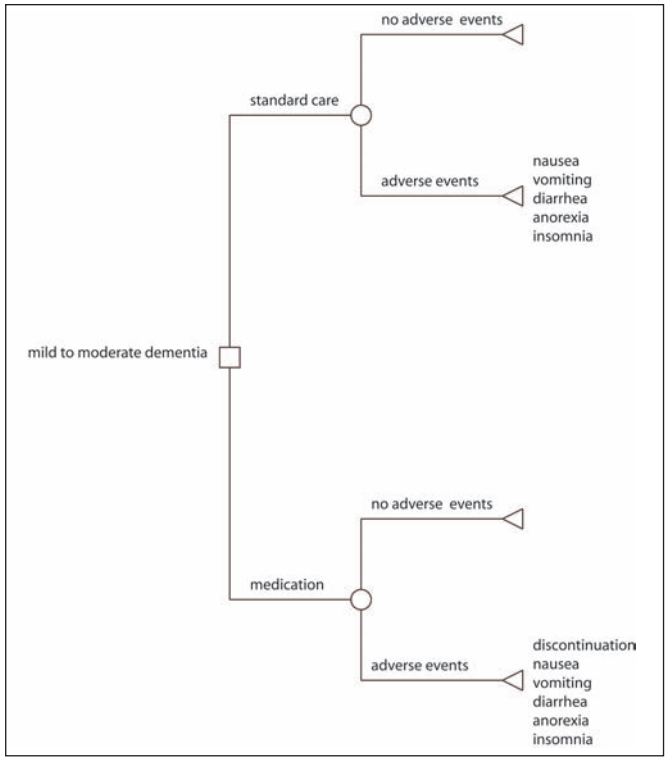

Figure 1: *Schematic representation of the decision model. The model begins with the decision to treat mild to moderate vascular dementia with medication or standard care (square node). Medication options include: 1) donepezil 5 mg daily, 2) donepezil 10 mg daily, 3) galantamine 16-24 mg daily, 4) rivastigmine flexible dosing up to 6 mg twice daily, and 5) memantine 10 mg twice daily. Primary treatment determines the probability of adverse events (circular uncertainty node). The triangle signifies the costs and health effects associated with the full sequence of events within a particular path.*

aged 65-74, to 4.8% in those age 85 and older.[3] The Canadian Collaborative Cohort of Related Dementias (ACCORD) study which described the distribution of individuals referred from the community to dementia clinics in Canada noted that among those with dementia, 8.7% had vascular dementia.[4]

Evidence indicates that a cholinergic deficit, similar to that seen in Alzheimer's disease (AD), may be associated with vascular dementia,[5] leading to the hypothesis that these patients may benefit from treatment with cholinesterase inhibitors. In addition, it is increasingly recognized that AD frequently co-exists with vascular dementia. As such, clinical trials of donepezil, rivastigmine and galantamine have been conducted in patients with vascular dementia.[6-9]

Since excessive N-methyl-D-aspartic acid (NMDA) stimulation induced by ischemia leads to excitotoxicity,[10] agents that block pathological stimulation of NMDA receptors might be anticipated to protect against further cortical neurodegeneration, normalize impaired glutamatergic neuro-transmission and lead to symptomatic improvement in vascular dementia.[11] This led to clinical trials of memantine, a moderate-affinity uncompetitive NMDA antagonist.[12-13]

A systematic review of published and unpublished randomized, double-blinded, placebo-controlled trials of cholinesterase inhibitors (donepezil, rivastigmine, and galantamine) and memantine concluded that there were small benefits in cognition in patients with mild to moderate vascular dementia over 24-28 weeks, as measured by the AD Assessment Scale-cognitive (ADAS-Cog) subscale.[14] Total scores on the cognitive subscale range from 0 to 70, where higher scores indicate more impairment. The review also found that compared with placebo, more dropouts and adverse events (anorexia, nausea, vomiting, diarrhea, and insomnia) occurred with the cholinesterase inhibitors, but not with memantine.[14] Donepezil has been approved for vascular dementia by regulatory agencies in many countries, but along with the other drugs, is yet to be approved for this indication in Canada. Furthermore, the latest Canadian Consensus Conference on the Diagnosis and Treatment of Dementia guidelines states that donepezil can be considered a treatment option for vascular dementia (Grade B, Level 1).[15] Even if the drugs meet regulatory approval, it is not clear whether the associated benefits and harms are a cost-effective use of Canada's healthcare resources.

The objectives of this study were to derive incremental cost-effectiveness ratios (ICERs) from a societal perspective in a Canadian healthcare setting. To our knowledge, our model is the first to study the cost-effectiveness of cholinesterase inhibitors and memantine in vascular dementia.

Table 1: Estimates of incremental effectiveness used in the decision model

Intervention	WMD in the ADAS-Cog Subscale (95% CI)*
donepezil 5 mg daily vs. placebo (24 weeks)	-1.15 (-1.65 to -0.64)
donepezil 10 mg daily vs. placebo (24 weeks)	-2.17 (-2.98 to -1.35)
galantamine 8-12 mg twice daily vs. placebo (24 weeks)	-1.60 (-2.39 to -0.80)
rivastigmine 6 mg twice daily vs. placebo (24 weeks)	-1.10 (-2.15 to -0.05)
memantine 10 mg twice daily vs. placebo (28 weeks)	-1.86 (-2.79 to -0.94)

* negative values indicate an improvement; WMD = weighted mean difference; ADAS-Cog subscale = Alzheimer's disease assessment scale-cognitive subscale; A normal distribution was used in probabilistic sensitivity analysis; Source: Kavirajan et al[14]

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Table 2: Estimates for clinical probabilities in the decision model

Event	Probability of Event (%)				
	donepezil 5 mg vs placebo	donepezil 10 mg vs placebo	galantamine 8-12 mg b.i.d. vs placebo†	rivastigmine 6 mg b.i.d. vs placebo	memantine 10 mg b.i.d. vs placebo
discontinuation	19.0 vs 15.8	26.4 vs 15.8	24.4 vs 15.7	24.7 vs 13.9	19.1 vs 18.4
nausea	9.8 vs 7.4	16.3 vs 7.4	18.2 vs 5.3	26.4 vs 3.8	4.8 vs 3.2
vomiting	5.7 vs 5.6	6.4 vs 5.6	10.3 vs 3.2	22.0 vs 2.3	n/a
diarrhea	14.5 vs 10.2	16.6 vs 10.2	8.6 vs 5.8	9.1 vs 4.4	4.1 vs 3.5
anorexia	6.9 vs 3.6	8.6 vs 3.6	5.4 vs 1.2	5.2 vs 1.7	n/a
insomnia	10.6 vs 5.2	9.8 vs 5.2	4.8 vs 1.5	4.4 vs 3.2	2.7 vs 6.7

Source: Kavirajan et al[14]; Beta distributions were used in the probabilistic sensitivity analysis; † vascular dementia and Alzheimer's disease; b.i.d. = bis in die (twice daily)

Methods

An incremental cost-effectiveness analysis, using a decision analysis model, was used to derive ICERs. Incremental cost-effectiveness ratios were expressed as the incremental cost per unit decrease in the ADAS-cog subscale that would result from using a cholinesterase inhibitor or memantine compared to standard care in the management of mild to moderate vascular dementia. Standard care, in Canada, does not include the use of cholinesterase inhibitors or memantine, as neither class of medication has yet been approved for vascular dementia by regulatory agencies. Figure 1 outlines the structure of the decision model; it illustrates the clinical problem, treatment strategies, and patient outcomes. Medication options considered were: 1) donepezil 5 mg once a day, 2) donepezil 10 mg once a day, 3) galantamine 16-24 mg daily, 4) rivastigmine flexible dosing up to 6 mg twice daily, and 5) memantine 10 mg twice daily, based on doses studied in clinical trials included in the systematic review.[14]

The target population included patients with mild to moderate vascular dementia, as diagnosed by standard criteria (National Institute for Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences [NINDS-AIREN][16], Diagnostic and Statistical Manual of Mental Disorders third edition revised [DSM-III-R][17], or fourth edition [DSM-IV]).[18]

Base-case estimates for clinical probabilities, costs, and effectiveness are listed in Tables 1-3. We extracted estimates of effectiveness and clinical probabilities of adverse events from a published systematic review of randomized, parallel-group, double-blinded, placebo-controlled clinical trials of marketed cholinesterase inhibitors (donepezil, rivastigmine, galantamine) or memantine.[14] Stroke was not included because data was not available for all therapeutic alternatives, and stroke is considered part of the natural history of vascular dementia rather than an outcome which is altered by treatment. Direct comparison of the benefits and harms for individual drugs were made from indirect comparisons of placebo controlled studies. To adjust for differences in trial populations, relative risks were derived for each drug, and probabilities calculated using a common placebo calculated as the average probability of each event from all trials. We estimated direct costs associated with the management of vascular dementia by adding costs of pharmaceuticals and physician services. A discount rate was not applied since the model was for a 24-28 week time horizon, consistent with the duration of the clinical trials. The cost of the cholinesterase inhibitors and memantine were estimated from the prescribed dosage, with unit prices obtained from the British Columbia PharmaCare program and a large retail pharmacy, respectively.

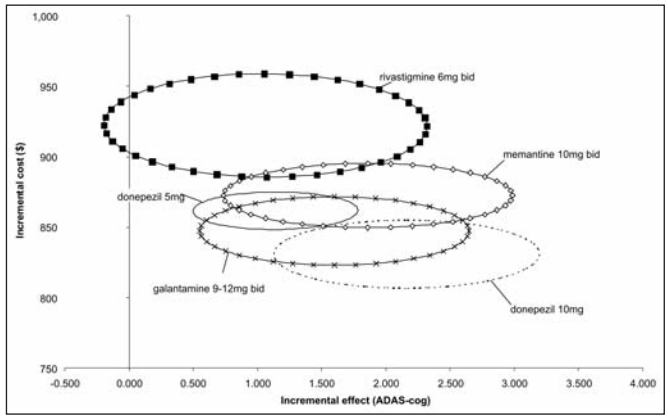

Figure 2: *Cost-effectiveness ellipses. Each ellipse represents the 95% confidence interval of the cost and effect for each treatment. The size of each ellipse represents the uncertainty in the estimates.*

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Table 3: Estimates for cost parameters used in the decision model

Drug	Cost
donepezil 5 mg daily	$147.22 for 30 tablets
donepezil 10 mg daily	$147.22 for 30 tablets
galantamine 16-24 mg daily	$147.34 for 30 tablets
rivastigmine 6 mg twice daily	$162.43 for 60 tablets
memantine 10 mg twice daily	$147.52 for 60 tablets
pharmacy dispensing fee	$5.00 per month
physician visit for medication monitoring or assessment of adverse event	$32.08 per visit

Fixed distributions were used in the probabilistic sensitivity analysis

A physician visit every 12 weeks for treatment monitoring was assumed for all patients receiving medication. Minor adverse events were assumed to be managed through a single visit to the general practitioner. Costs of physician visits were based on the Medical Services Plan of British Columbia fees.

All costs were reported in 2008 Canadian dollars. We expressed our results in incremental cost-effectiveness ratios (dollars per unit decrease in the ADAS-cog subscale). Confidence intervals around costs and effects were estimated with a probabilistic sensitivity analysis using a Monte Carlo simulation.[19] A normal distribution was fitted for the weighted mean difference in the ADAS-Cog subscale, a fixed distribution was used for the cost parameters, and beta distributions were used for the incidence of adverse events. Probability distributions were sampled 10,000 times for each scenario. Microsoft Office Excel 2003 was used to perform the analysis.

Results

The systematic review identified incremental benefits in the ADAS-cog subscale for all medications compared to standard care (Table 1). The incremental effect was greatest for donepezil 10 mg daily.

The expected incremental costs for all medication strategies, were higher than standard care (Table 4). When comparing the cost-effectiveness, donepezil 10 mg was found to be the most cost-effective treatment with an expected ICER of $400.64 (95%CI $281.1-$596.35) per unit decline in the ADAS-cog subscale. All other treatments were dominated by donepezil 10 mg, that is, cost more and had less effect (Table 4). Uncertainty in costs and effects varied between treatments based predominantly on the sample sizes of the trials the estimates were based on (Figure 2).

Discussion

This is the first model to examine the cost-effectiveness of cholinesterase inhibitors and memantine in vascular dementia. Under the assumptions of this analysis, we found that treatment with cholinesterase inhibitors or memantine was more effective but also more costly than standard care in patients with mild to moderate vascular dementia. Of the available treatments, the donepezil 10 mg strategy was the most cost-effective. However, other reasons may guide the choice of treatment apart from the cost-effectiveness, including patient choice and physician experience with particular therapies.

Our analysis has several limitations. First, generic multi-attribute preference-weighted health state classifications have not yet been applied to a population of patients with vascular dementia; thus, the analysis was restricted to the clinical effectiveness parameters used in clinical trials rather than health utilities which would have enabled a cost-utility analysis. Second, the evidence on the effects and harms come from separate trials, so confounding could be introduced into the comparisons. Third, our model is limited to a time horizon of 24-28 weeks according to data available from clinical trials; as such, it does not contain data on later outcomes and major costs such as use of community support services and long-term care.

Table 4: Incremental cost effectiveness ratios (cost per unit decrease in the ADAS-cog subscale)

Drug	Incremental cost (95%CI), $	Incremental effect (95% CI)	ICER (95%CI), $
donepezil 5 mg	861.7 (850.59-872.61)	1.14 (0.63-1.66)	
donepezil 10 mg	830.87 (811.84-850.24)	2.16 (1.38-2.97)	400.64 (281.1-596.35)
galantamine 16-24 mg daily	847.34 (828.52-866.18)	1.6 (0.75-2.43)	
rivastigmine 6 mg b.i.d.	922.24 (893.31-949.63)	1.06 (0.01-2.06)	
memantine 10 mg b.i.d.	872.45 (853.54-890.35)	1.86 (1.03-2.77)	

ICER = incremental cost effectiveness ratio; b.i.d. = bis in die (twice daily)

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Fourth, there is concern that the ADAS-cog subscale may not sufficiently capture the specific deficits of executive function in patients with vascular dementia and therefore may underestimate the degree of their impairment and underestimate the effect of treatment. Fifth, many of the people recruited into the trials included in the meta-analysis possibly did not have strict vascular dementia but a mixed pathology.[20] Last, missing information on the probabilities of specific adverse events with memantine limits comparisons between medication strategies.

In summary, by synthesizing the best available evidence on effectiveness, complications, and costs, we found that treatment with cholinesterase inhibitors or memantine were more costly than standard care alone. The benefits in cognition in patients with mild to moderate vascular dementia from the treatments are small. Canadian guidelines recommend that donepezil can be considered a treatment option for vascular dementia[15]. If the cholinesterase inhibitors eventually meet regulatory approval for this indication, policymakers should consider funding donepezil 10 mg daily as it is the dominant choice from the perspective of economic evaluation.

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