Diagnosis and treatment of dementia: Introduction

Introducing a series based on the Third Canadian Consensus Conference on the Diagnosis and Treatment of Dementia

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During the next 3 years, a demographic milestone will be reached across North America as baby boomers, who are currently in their late 50s, begin to reach 65 years of age. The proportion of the Canadian population aged 65 or older will rise from 11.6% in 1991 to 16% in 2016 and will reach 23% in 2041. As this demographic shift occurs, the health problems affecting elderly people will take centre stage as never before. The prevalence of dementia (both general types of dementia and Alzheimer disease) dramatically increases with age. The prevalence of Alzheimer disease is 1% among people aged 65–74 years, 6.9% among those 75–84 years and 26% among those aged 85 years and older.[1] Although the evidence is dated, it is expected that in the next decade there will be a large increase in the number of patients who present with memory loss and dementia in Canada (Figure 1) and the United States. In Canada, there are 60 150 new cases of dementia each year,[2] and there are currently about 450 000 people with all forms of dementia. This figure is expected to double over the next 30 years.[1,3] The increase in vascular dementia will be less dramatic compared with all types of dementia (because of improved hypertension control). The prevalence of Alzheimer disease is expected to increase sharply unless dramatic new preventative therapies emerge.

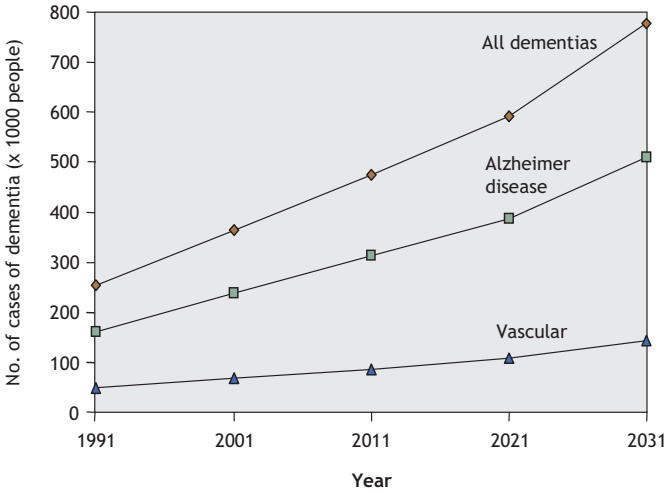

Figure 1: Projected prevalence of all dementias, Alzheimer disease and vascular dementia in Canada.[2,3]

Box 1: General criteria for diagnosing dementia[4]

A. The development of multiple cognitive deficits manifested by both:

1. Memory impairment (impaired ability to learn new information or to recall previously learned information).
2. One or more of the following cognitive disturbances:
   - aphasia (language disturbance)
   - apraxia (impaired ability to carry out motor activities despite intact motor function)
   - agnosia (failure to recognize or identify objects despite intact sensory function)
   - disturbance in executive function (e.g., planning, organizing, sequencing, abstracting)

B. The cognitive deficits in criteria A1 and A2 each cause major impairment in social or occupational functioning and represent a substantial decline from a previous level of functioning.

C. The deficits do not occur exclusively during the course of a delirium.

The dementias are a family of diseases defined in clinical terms (Box 1). Our understanding of the dementia subcategories continues to evolve as the fields of imaging and neuropathology supply new levels of detail. Forty years ago, dementias were classified as cortical or subcortical.[5] Such localization approaches are highly inaccurate but serve to stress the difference between dementias without motor features (e.g., Alzheimer disease, frontotemporal dementias) and most other dementias (characterized by the presence of accompanying motor and gait abnormalities). Figure 2 shows the types of dementia commonly seen in Canadian dementia clinics.[6] In this type of classification, mixed dementia (usually Alzheimer disease and vascular dementia) is common. Individuals with mixed dementias have 2 separate brain conditions (degenerative disease and vascular insults) that are synergistic in producing clinical symptoms of dementia at an earlier age than either alone.[7]

Alzheimer disease is not only devastating to both patients and affected families but also is a considerable financial bur-

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den on society, particularly as the disease progresses. It is estimated that the annual economic burden is Can$10 000 for each person with mild Alzheimer disease and $37 000 for severe Alzheimer disease.[8] For every person with dementia who does not live in a long-term care facility, there is also the burden of caregiving, which usually falls on the patient's spouse or children. Supporting caregivers and managing and treating their stress will also be increasing problems for Canadian physicians.

New developments in dementia

Following publication of the recommendations from the Second Canadian Consensus Conference on Dementia in 1999,[9,10] there have been developments in many fields, including biology and genetics, risk assessment, and management. There have been substantial improvements in neuroimaging, such as magnetic resonance imaging (MRI) hippocampal volume measures,[11] and positron emission tomography (PET) scanning with flourodeoxyglucose and amyloid ligands.[12] Other developments include the recognition of the potential role of homocysteine in the pathogenesis of Alzheimer disease[13] and the discovery of new genes associated with sporadic, late-onset Alzheimer disease[14] and a form of frontotemporal dementia.[15,16] The recognition that vascular risk factors (e.g., hypertension, hyperlipidemia) increase the likelihood of Alzheimer disease and vascular dementia offers enhanced opportunities for prevention of dementia. These recent advances raise questions about the optimal approach for diagnosing dementia.

In addition to improvements in diagnosing dementia, we have also made progress in its management. New types of nonpharmacologic treatments have been developed and studied, despite the inherent difficulties of research in this area. Guidelines on dementia and driving have been introduced. Cholinesterase inhibitors have been widely adopted into practice, although their usefulness continues to be debated. Memantine (Ebixa) has been introduced in Canada. This antagonist to glutamate *N*-methyl-D-aspartate (NMDA) receptors has a small beneficial effect in cases of moderate to severe Alzheimer disease, but it has not been shown to be effective in the mild stages.[17] Many physicians remain uncertain about its place in Alzheimer disease therapy. The use of vitamin E as a therapeutic agent received dissenting support at the second consensus conference; however, its routine use was not recommended in the published guidelines. Since then, vitamin E has come under attack as a therapeutic intervention.

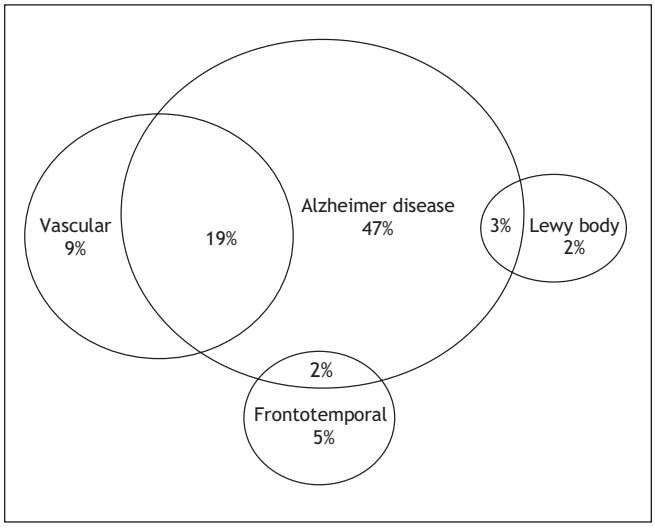

Figure 2: Types of dementia commonly seen in Canadian memory clinics.[6] Note: Other mixed types of dementia make up 10% of the total number of cases.

The Third Canadian Consensus Conference on the Diagnosis and Treatment of Dementia

Faced with significant advances and new evidence on existing diagnostics and therapeutics, the Third Canadian Consensus Conference on the Diagnosis and Treatment of Dementia (CCCDTD3) was held in March 2006. The organization, planning and structure of the conference adhered as much as possible to the guidelines established by the Appraisal of Guidelines Research and Evaluation (AGREE) collaboration,[18] and we met 19 of the 23 criteria (Appendix 1). A steering committee that included nationally eminent experts in different aspects of dementia organized this meeting.

The conference was funded by government, industry and not-for-profit charities (Appendix 2). The total contribution of pharmaceutical companies was less than 50% of the total cost of the conference. All grants were unrestricted, and no organization or company had any input into the form or content of the recommendations.

Guideline-creation process

We established communication with the College of Family Physicians of Canada early in the process, and a representative of the College was included in the organizing committee. Participants in the working groups were chosen because of their expertise in dementia or a related area and their reputation as a national leader. Participants were also chosen based on their reputation for delivering high-quality work and for being open-minded and collaborative. We included a family physician in each working group to review the recommendations from a family-practice perspective. Each participant provided a written conflict-of-interest statement.

Each working group performed literature searches, prepared background papers and agreed to a series of draft recommendations. The papers and recommendations were posted to a website, and feedback was solicited from all participants. This process lasted several months. We performed a standardized analysis of the quality of the evidence for therapy, which included a rating of the quality of the studies by use of the Jadad scale[19] and such quantitative aspects as statistical significance and magnitude of effects.[20]

Box 2: Levels of evidence at the Third Canadian Consensus Conference on the Diagnosis and Treatment of Dementia[21]

1. Evidence obtained from at least 1 properly randomized controlled trial.
2.1. Evidence obtained from well-designed controlled trials without randomization, or
2.2. Evidence obtained from well-designed cohort or case-control analytic studies preferably from more than 1 centre or research group, or
2.3. Evidence obtained from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments are included in this category.
3. Opinions of respected authorities based on clinical experience, descriptive studies or reports of expert committees.

The quality of the available evidence was graded using a system adapted from the Canadian Task Force on Preventive Health Care (Box 2, Box 3).[21] We assessed the strength of the recommendations using the system that had been used in the Second Canadian Consensus Conference on Dementia.[9,22] Ideally, grade A and E recommendations were supported by level 1 evidence; however, level 2 evidence was sometimes deemed sufficient. A grade C recommendation did not imply that the manoeuvre was useless or harmful. Instead, it meant that there was insufficient evidence to make a stronger recommendation or that studies to date have reported conflicting results. In the series of articles to be published in *CMAJ* in the coming months, the grading and strength of supporting evidence is given.

Conference participants read the background papers prepared by each working group and voted on the recommendations (80% of votes were required for consensus). Recommendations that did not achieve consensus were either modified (and the amended recommendation brought forward for further discussion) or discarded. In 5 cases, the final vote on the amended recommendation received between 60%–80% of votes. These recommendations were stated to have achieved only weak consensus.

At a 2-day meeting attended by all members of the working groups (including 2 family practitioners designated by the College of Family Physicians of Canada, delegates from the Canadian Institutes of Health Research and the Alzheimer Society of Canada, and observers from other partners including pharmaceutical companies), each working group provided a brief overview, followed by a presentation, discussion and voting on each modified recommendation. Voting was open and transparent, and the process for formulating recommendations was outlined in detail before the conference. Several recommendations had to be reworked to achieve group approval.

A total of 215 recommendations were initially posted on the website. Of these, 146 were ultimately approved with strong consensus. Five achieved weak consensus, and the remaining recommendations were rejected (or modified and incorporated into other recommendations). This process (and the recommendation list) was unique in its scope and breadth, its success at achieving agreement among physicians and specialists from different domains, and its determination to develop practical guidelines and recommendations that are relevant to general physicians. The full set of recommendations is available on the websites of the Third Canadian Consensus Conference on the Diagnosis and Treatment of Dementia (www.cccdtd.ca) and the Alzheimer Society of Canada (www.alzheimer.ca).

Dissemination of the recommendations

In the coming months, *CMAJ* will present a 5-part case-based series highlighting new advances and their role in practice. This series will provide clinicians with a practical, evidence-based approach to the management of dementia. The series focuses on the following topics:

1. Risk factors and prevention of Alzheimer disease and dementia. Some of the genes involved in early- and late-onset Alzheimer disease are known: should genetic testing be performed? We also have considerable knowledge of the environmental risk factors for dementia. What advice should physicians give to their patients who want to preserve their memory into old age?
2. Investigating and diagnosing dementia. Alzheimer disease is the most serious illness for which we lack a simple blood test, definitive imaging or biopsy guidance for diagnosis. What current tests should family physicians and specialists use in diagnosis? What lies in the future?
3. Mild cognitive impairment and cognitive impairment no dementia. Attempts have now been made to define, diagnose and manage these early stages of mild memory loss. How do these developments affect clinical practice?
4. Managing mild and moderate dementia. Given the recent progress in symptomatic therapy, improved knowledge of the vascular aspects of dementia and new approaches to changing progression, what treatments are recommended?
5. Managing severe dementia. What pharmacologic and non-pharmacologic approaches should be used to manage cognitive and behavioural problems at this stage of illness?

Knowledge gaps

Although this series of articles defines the current status of management, there is no doubt that there are knowledge

Box 3: Grades indicating the strength of recommendations from the Third Canadian Consensus Conference on the Diagnosis and Treatment of Dementia[9,22]

A. There is good evidence to support this manoeuvre.
B. There is fair evidence to support this manoeuvre.
C. There is insufficient evidence to recommend for or against this manoeuvre but recommendations may be made on other grounds.
D. There is a fair evidence to recommend against this procedure.
E. There is good evidence to recommend against this procedure.

Box 4: Knowledge gaps

- Estimates of incidence are limited by the lack of recent prospective inception-cohort studies.
- Known risk factors have not been studied in longitudinal primary-prevention studies.
- Further research is required to better understand the genetic contribution to late-onset Alzheimer disease.
- Widely accepted, validated, easy-to-use diagnostic tools are not yet available to predict development of dementia.
- Therapeutic options remain limited and symptomatic.

gaps (Box 4) and that the future will bring more developments in the clinical care of dementia. Simple diagnostic and monitoring tests are sorely needed. A decade from now, we hope to have a "cognitive blood-pressure cuff" or a biomarker that allows much earlier diagnosis of Alzheimer disease. We hope to have clear nonpharmacologic therapeutic approaches and more effective therapies to modulate and prevent this disease. We also hope to have improved medical manpower and reformed health-care funding to allow physicians more time to devote to diagnosing, managing and treating elderly patients with dementia as well providing support to their caregivers.

As with all guidelines for major diseases, it is difficult to identify and synthesize large bodies of literature. It is even more difficult to draw clear conclusions and make recommendations when the evidence is either limited or altogether lacking. Although we made every attempt to ensure that our methodology was rigorous, that our evidence base complete and that our recommendations were made using an unbiased and transparent decision-making process, expert opinion and judgement were frequently required. Some of our recommendations may be dated as more recent information becomes available, and quite frequently, clear unambiguous recommendations could not be made. We also recognize that implementation of all 146 recommendations may be difficult because of unrecognized barriers.

We chose not to develop separate sets of recommendations for different levels of specialization. In addition, this series of articles has a clear focus on Alzheimer and vascular dementia, rather than on more rare forms of dementia (e.g., Lewy body disease, normal pressure hydrocephalus). The background articles for the recommendations provide considerably more detail about less frequent forms of dementia and their management.

It is our hope that these guidelines and their dissemination through *CMAJ* will improve the assessment of risk, diagnosis and care of patients with dementia. We encourage *CMAJ* readers to provide feedback to our working group, so that further recommendations can be based on a wide appreciation of needs among health care professionals.

This article has been peer reviewed.

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Editor's Note: The 18 background papers with supporting evidence for the recommendations were published in the October 2007 issue of *Alzheimer's and Dementia* and are available at www.alzheimersanddementia.org. These articles are also freely available at www.cccdtd.ca (through agreement with Elsevier).

REFERENCES

1. Canadian Study of Health and Aging: Risk factors for Alzheimer's disease in Canada. *Neurology* 1994;44:2073-80.
2. The incidence of dementia in Canada. The Canadian Study of Health and Aging Working Group. *Neurology* 2000;55:66-73.
3. Canadian study of health and aging: study methods and prevalence of dementia. *CMAJ* 1994;150:899-913.
4. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, 4th ed.* Washington: The Association; 1994.
5. Wells CE. Differential diagnosis of Alzheimer's dementia: affective disorder. In: Reisberg B, ed. *Alzheimer's Disease: The Standard Reference.* New York: Free Press; 1983. p.193-7.
6. Feldman H, Levy AR, Hsiung GY, et al. A Canadian cohort study of cognitive impairment and related dementias (ACCORD): study methods and baseline results. *Neuroepidemiology* 2003;22:265-74.
7. Snowdon DA, Greiner LH, Mortimer JA, et al. Brain infarction and the clinical expression of Alzheimer disease. The Nun Study. *JAMA* 1997;277:813-7.
8. Hux MJ, O'Brien BJ, Iskedjian M, et al. Relation between severity of Alzheimer's disease and costs of caring. *CMAJ* 1998;159:457-65.
9. Patterson CJ, Gauthier S, Bergman H, et al. The recognition, assessment and management of dementing disorders: conclusions from the Canadian Consensus Conference on Dementia. *CMAJ* 1999;160(Suppl):S1-15.
10. Patterson CJ, Gauthier S, Bergman H, et al. Canadian Consensus Conference on Dementia: a physician's guide to using the recommendations. *CMAJ* 1999;160: 1738-42.
11. Jack CR Jr, Petersen RC, Xu Y, et al. Rates of hippocampal atrophy correlate with change in clinical status in aging and AD. *Neurology* 2000;55:484-9.
12. Klunk WE, Price JC, DeKosky ST, et al. The applications of amyloid-imaging to the diagnosis and treatment of Alzheimer's disease. *Alzheimers Demen* 2005;1(Suppl):5.
13. Seshadri S, Beiser A, Selhub J, et al. Plasma homocysteine as a risk factor for dementia and Alzheimer's disease. *N Engl J Med* 2002; 346:476-83.
14. Rogaeva E, Meng Y, Lee JH, et al. The neuronal sortilin-related receptor SORL1 is genetically associated with Alzheimer disease. *Nat Genet* 2007;39:168-77.
15. Baker M, Mackenzie IR, Pickering-Brown SM, et al. Mutations in progranulin cause tau-negative frontotemporal dementia linked to chromosome 17. *Nature* 2006;442:916-9.
16. Mackenzie IR, Baker M, West G, et al. A family with tau-negative frontotemporal dementia and neuronal intranuclear inclusions linked to chromosome 17. *Brain* 2006;129:853-67.
17. Areosa SA, Sherriff F, McShane R. Memantine for dementia. Cochrane Database Systematic Reviews 2005 Jul 20; (3): CD003154.
18. The Appraisal of Guidelines Research and Evaluation (AGREE) Collaboration. The AGREE Instrument. London (UK): The Collaboration; 2001. Available: www.agreecollaboration.org/pdf/agreeinstrumentfinal.pdf (accessed 2007 Dec 20).
19. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996;17:1-12.
20. Natural Standard. Explanation of Columns in Natural Standard Evidence Table. Cambridge (MA): The Standard. www.naturalstandard.com/explanation_columns.html (accessed 2007 Dec 20).
21. Woolf SH, Battista RN, Anderson GM, et al. Assessing the clinical effectiveness of preventive maneuvers: analytic principles and systematic methods in reviewing evidence and developing clinical practice recommendations. A report by the Canadian Task Force on the Periodic Health Examination. *J Clin Epidemiol* 1990;43:891-905.
22. Patterson C, Gauthier S, Bergman H, et al. The recognition, assessment and management of dementing disorders: conclusions from the Canadian Consensus Conference on Dementia. *Can J Neurol Sci* 2001;28(Suppl 1):S3-16.

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Appendix 1: Criteria of the Appraisal of Guidelines for Research and Evaluation (AGREE) Instrument[18] addressed by the Third Canadian Consensus Conference on the Diagnosis and Treatment of Dementia

Criteria	Addressed	Not addressed
Scope and purpose		
The overall objective(s) of the guideline is (are) specifically described	X	
The clinical question(s) covered by the guideline is (are) specifically described	X	
The patients to whom the guideline is meant to apply are specifically described	X	
Stakeholder involvement		
The guideline development group includes individuals from all the relevant professional groups	X	
The patients' views and preferences have been sought		X
The target users of the guideline are clearly defined	X	
The guideline has been piloted among target users	X	
Rigour of development		
Systematic methods were used to search for evidence	X	
The criteria for selecting the evidence are clearly described	X	
The methods used for formulating the recommendations are clearly described	X	
The health benefits, side effects and risks have been considered in formulating the recommendation	X	
There is an explicit link between the recommendations and the supporting evidence	X	
The guideline has been externally reviewed by experts prior to its publication	X	
A procedure for updating the guideline is provided		X
Clarity and presentation		
The recommendations are specific and unambiguous	X	
The different options for management of the condition are clearly presented	X	
Key recommendations are easily identifiable	X	
The guideline is supported with tools for application	X	
Applicability		
The potential organizational barriers in applying the recommendations have been discussed	X	
The potential cost implications of applying the recommendations have been discussed		X
The guideline presents key review criteria for monitoring and/or audit purposes		X
Editorial independence		
The guideline is editorially independent from the funding body	X	
Conflicts of interest of guideline development members have been recorded	X	

Appendix 2: Funding sources for the Third Canadian Consensus Conference on Diagnosis and Treatment of Dementia

Financial or in-kind support was obtained from:

- Canadian Institutes of Health Research
- Fonds de la recherche en santé du Québec
- Alzheimer Society of Canada,
- Consortium of Canadian Centres for Clinical Cognitive Research
- Canadian Neurological Society
- College of Family Physicians of Canada
- Canadian Academy of Geriatric Psychiatrists
- Quebec Research Network on Aging
- Canadian Geriatric Society.
- Pharmaceutical companies (unrestricted contributions of $10 000 each): Lundbeck Canada, Janssen-Ortho Inc., Pfizer Canada, Novartis, Neurochem Inc., Sanofi-Aventis, Boehringer Ingelheim.

Steering Committee members (alphabetical order): *Dr. Howard Bergman (Joseph Kaufmann Professor of Geriatric Medicine, McGill University; president of the Canadian Geriatric Society; director of the Quebec Research Network on Aging); Dr. Howard Chertkow (professor of Neurology and Geriatric Medicine, McGill University; past president of the Consortium of Canadian Centres for Clinical Cognitive Research; chair of the steering committee); Dr. John W. Feightner (family physician; professor of Family Practice, University of Western Ontario); Dr. Howard Feldman (professor and head of the Division of Neurology, University of British Columbia; liaison to the Canadian Neurological Society); Dr. Serge G. Gauthier (professor of Neurology, Medicine, and Psychiatry, McGill University; chief of the Alzheimer's disease research unit at the McGill Centre for Studies in Aging); Dr. Nathan Herrmann (geriatric psychiatrist; professor and director of Geriatric Psychiatry, Sunnybrook Hospital, University of Toronto; liaison to the Canadian Academy of Geriatric Psychiatry); Dr. David Hogan (Brenda Stafford Foundation Chair; professor in Geriatric Medicine, University of Calgary); Dr. Yves Joanette (neuropsychology and speech-language pathologist; directeur, Centre de recherche de l'Institut universitaire de gériatrie de Montréal, Université de Montréal); Dr. Christopher J. Patterson (professor of Geriatric Medicine; McMaster University).*

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