Fourth Canadian Consensus Conference on the Diagnosis and Treatment of Dementia

Recommendations for family physicians

Ainsley Moore MSc MD CCFP  Christopher Patterson MD FRCP FACP FRCPC FACP( Glasg)  Linda Lee MD MCIs(FM) CCFP FCFP  Isabelle Vedel MD PhD  Howard Bergman MD FCP FRCPC

Abstract

Objective
To revise diagnostic strategies for Alzheimer disease (AD), update recommendations on symptomatic treatment of dementia, and provide an approach to rapidly progressive and early-onset dementias.

Composition of the committee
Experts and delegates representing relevant disciplines from diverse regions across Canada discussed and agreed upon revisions to the 2006 guidelines.

Methods
The GRADE (grading of recommendations, assessment, development, and evaluation) system was used to evaluate consensus on recommendations, which was defined as when 80% or more of participants voted for the recommendation. Evidence grades are reported where possible.

Report
Important for FPs, despite advances in liquid biomarkers and neuroimaging, the diagnosis of dementia in Canada remains fundamentally clinical. New core clinical criteria for the diagnosis of AD now recognize less common, nonamnestic forms. Early-onset dementia, a rare but important condition, should prompt referral to specialists with access to genetic counselors. Rapidly progressive dementia, poorly defined in the literature, is described to facilitate detection of this rare but important condition. There are new expanded indications for cholinesterase inhibitors beyond AD, as well as guidelines for their discontinuation, which had not been previously described. New evidence regarding use of memantine, antidepressants, and other psychotropic medications in dementia care is presented.

Conclusion
Several recommendations from the Fourth Canadian Consensus Conference on the Diagnosis and Treatment of Dementia are relevant to FPs. For guidelines to remain useful, family physicians should participate in all stages of the ongoing development process, including topic selection.

The rising prevalence of dementia imposes substantial challenges for patients, families, and societies. In Canada, Alzheimer disease (AD), the most common cause of dementia, will increase from the current 500,000 cases to 1.1 million cases by 2038. The World Health Organization urges countries to view dementia as a critical public health priority and notes that dementia “poses one of the greatest societal challenges for the 21st century.”

The Canadian Consensus Conference on the Diagnosis and Treatment of Dementia (CCCDTD) has proposed many recommendations to guide Canadian FPs. Indeed, 3 previous CCCDTDs recommended that diagnosis and management of patients with dementia

EDITOR’S KEY POINTS

• Despite notable technologic advances, diagnosis of Alzheimer disease (AD) remains fundamentally clinical. However, it is critical for FPs to be aware of advancing technologies, such as neuroimaging and measurement of biomarkers such as amyloid-β1-42, τ, and hyperphosphorylated τ, that are rapidly changing how dementia is conceptualized and discussed.

• Based on convincing trials showing that cholinesterase inhibitors have efficacy in conditions other than mild to moderate AD, these drugs should be considered in AD with a component of cerebrovascular disease, Parkinson dementia, and all stages of AD. Valproate should not be used for agitation and aggression in patients with AD.

• For guideline updates to remain relevant, FPs should contribute to all stages of development, including topic selection. Future topics should address challenges of delivering front-line, comprehensive, and holistic care for families, caregivers, and patients living with dementia.
should mainly be the responsibility of primary health care and this remains implicitly valid. Optimal use of these guidelines has been partly limited by lack of citizen, caregiver, and FP participation in the guideline development process; scepticism regarding pharmaceutical sponsorship; and overly lengthy and complex guidelines. The Fourth CCCDTD (CCCDTD4) has responded to many of these challenges, and the objective of this report is to summarize relevant recommendations for FPs from this conference. The intention is to provide a useful update informing Canadian FPs of recent advances in dementia care that are based on the best available evidence.

Several factors prompted the CCCDTD4. Dramatic advances in neuroimaging and use of biomarkers have stimulated new ways of conceptualizing AD even in the absence of clinical symptoms. In 2011, this compelled the US National Institute on Aging and the Alzheimer’s Association (NIA-AA) to jointly propose new diagnostic criteria for research purposes. A catalyst for the CCCDTD4 was concern about migration of such investigations into clinical care before the diagnostic and prognostic values were known, and consideration of the substantial ethical and financial implications of premature clinical use. Therefore, an objective of the committee was to update the previous diagnostic approach to AD based on these considerations. Additional topics included updated evidence on memantine, antidepressants, and other psychotropic medications in dementia, and guidelines for managing early-onset dementias and rapidly progressive dementias (RPDs). The conference assembled in Montreal, Que, on May 4 and 5, 2012.

Composition of the committee

An initial steering committee, composed of dementia experts in neurology, neuroimaging, biochemistry, geriatric medicine, biomedical ethics, and knowledge translation, convened in May 2011 to select topics, assign teams, and prepare background papers and preliminary recommendations for the full committee to review at the May 2012 conference.

At the conference, a broader group of disciplines was represented, including neurology, psychiatry, internal medicine, geriatric medicine, family medicine, clinical pharmacology, nuclear medicine, radiology, biochemistry, genetics, and bioethics. Participants from Vancouver, BC; Calgary, Alta; London, Ont; Hamilton, Ont; Toronto, Ont; Montreal, Que; Quebec city, Que; and Halifax, NS, attended. Delegates from the Canadian Academy of Geriatric Psychiatry, the Canadian Geriatrics Society, the College of Family Physicians of Canada, and the Alzheimer Society of Canada also attended. A memory clinic patient was invited but did not attend.

Sponsorship. Residual funding designated for knowledge translation from the 2006 Third CCCDTD covered the costs of CCCDTD4. Although original sources of these funds included pharmaceutical companies, temporal separation and intended use of funds insured there was no commercial influence on participant selection, topic choice, or preparation of background papers and recommendations. Two observers each from Pfizer Canada and Novartis were invited to the conference, in recognition of their support for previous consensus conferences. In-kind support was provided by the Canadian Institutes of Health Research, the Canadian Dementia Knowledge Translation Network (www.lifeandminds.ca), and the offices of Drs Serge Gauthier (McGill University in Montreal), Christopher Patterson (McMaster University in Hamilton), and Howard Chertkow (McGill University).

Methods

The GRADE (grading of recommendations, assessment, development, and evaluation) system was used to evaluate consensus on recommendations and codify the strength of recommendations (strong or weak) and levels of evidence (A to C). Evidence grades are reported where possible. The process was guided by the AGREE (Appraisal of Guidelines for Research and Evaluation) Collaboration (20 of the 23 criteria were met). Diagnostic criteria and definitions are presented in Box 1.

Complete background articles and draft recommendations were posted to a password-protected website, accessible to all conference participants, for review and comment before the conference. Recommendations were modified based on comments, revised, and posted for final online voting.

All participants had full access to the background articles and were encouraged to comment and vote on recommendations. Online voting closed 1 day before the conference. At the conference, each topic was briefly reviewed before formal voting on each recommendation took place. All participants (except for the 4 industry observers) voted.

Consensus was defined as 80% or more of participants voting for the recommendation.

Report

The complete list of recommendations is published elsewhere. Background papers providing the evidence and justification for each recommendation can be found at www.cccdtd.ca. Recommendations relevant to FPs are summarized in Box 2.

New diagnostic criteria and definitions. The committee endorsed the 2011 NIA-AA criteria and definitions for dementia, AD, and mild cognitive impairment (MCI) due to AD. Important for FPs, the diagnosis remains fundamentally clinical even with advancing technology designed to be used by health practitioners in all clinical settings without the use of advanced neuropsychiatric testing, neuroimaging, or cerebrospinal fluid (CSF) measures. While several changes to the core clinical criteria are based on advanced understanding...
Adoption of the criteria for all-cause dementia proposed by the NIA-AA working group in 2011

Adoption of the criteria for probable and possible AD proposed by the NIA-AA working group in 2011

- Diagnostic criteria for probable AD
  - Probable AD is diagnosed when the criteria for dementia are met, and symptoms have a gradual onset over months to years, not suddenly over hours or days, and there is clear worsening of cognition. Additionally, the initial and most prominent cognitive deficits are usually amnestic (associated with impairment in learning and recall of recently learned information) or less commonly nonamnestic (when language deficits are most prominent, eg, word-finding difficulties). Deficits should also occur in other domains such as visuospatial abilities (face or object recognition) and executive function (reasoning, judgment, problem solving). The diagnosis of probable AD should not be applied when substantial concomitant cerebrovascular disease is present.

- Diagnostic criteria for possible AD
  - A diagnosis of possible AD should be made when the criteria for AD are met (regarding the nature of cognitive deficits) but the disease follows an atypical course (eg, there is a sudden onset of cognitive impairment and cognitive decline is not gradual), or when criteria for AD are met but there is evidence of a mixed presentation, such as concomitant cerebrovascular disease, or the patient has clinical features of dementia with Lewy bodies, has another comorbidity (medical or neurologic), or is using medication that could have a substantial effect on cognition.

Adoption of the criteria for MCI by the NIA-AA working group in 2011

- MCI is diagnosed when there is concern regarding a decline in cognition reported by the patient, informant, or clinician, and there is objective evidence of cognitive deficits in 1 or more domains (typically memory) and most important there is preservation of independence in functional abilities. The differentiation of dementia from MCI rests on whether there is substantial interference in the ability to function at work or in usual daily activities. This is a clinical judgment. Further evaluation examines the pathogenesis of MCI, focusing on ruling out vascular, traumatic, and medical causes, and consideration of AD genetic factors.

Adoption of the 2011 American Heart Association–American Stroke Association recommendations for the diagnosis of vascular cognitive impairment


of typical clinical manifestations, the essential features (an acquired disorder of diffuse cognitive deficits, sufficient to interfere with daily function in the absence of delirium or serious depression) remain unchanged. The diagnosis of the most common form of AD (amnestic) is characterized by deficits in episodic memory (the ability to learn new information and recall recently learned information). The new definitions also recognize that memory impairment is not always the primary cognitive deficit in patients with AD. Although much less common, there are several nonamnestic presentations involving the pathophysiologic process of AD.

Box 1. Diagnostic criteria and definitions

Box 2. Recommendations

Neuroimaging
- In addition to previously recommended indications for structural imaging, a computed tomography scan or magnetic resonance imaging should be undertaken in the assessment of a person with cognitive impairment and unsuspected cerebrovascular disease, if it would change the clinical management.
- When faced with amyloid test results obtained outside Canada, physicians should be very cautious in their interpretation. Used in isolation this test cannot diagnose AD or MCI, or differentiate normal from abnormal aging. Consultation with a dementia specialist familiar with this test is recommended. Advising patients against undertaking such investigations is also recommended.

Liquid biomarkers
- Measuring CSF amyloid-β and τ levels is not recommended for clinical practice.

Early-onset dementia
- All patients with early-onset dementia should be referred to a memory clinic, preferably one with access to genetic counseling and testing when available.
- Physicians should be sensitive to the special issues associated with early-onset dementia, particularly in regard to loss of employment and access to support services appropriate for that age group.

RPD*
- It is suggested that RPD be defined as a condition that develops within 12 months after the appearance of first cognitive symptoms (grade 2C).
- After exclusion of delirium, it is suggested that individuals with suspected RPD be referred to physicians who are experienced with RPD and have access to the diagnostic facilities able to mount an organized and comprehensive diagnostic process (grade 2C).
- For individuals with AD, it is suggested that a decline of 3 or more points on the MMSE in 6 months, which identifies a group with a worse prognosis, is a signal to explore comorbid conditions and review pharmacologic management (grade 2B).

AD—Alzheimer disease, CSF—cerebrospinal fluid, MCI—mild cognitive impairment, MMSE—Mini-Mental State Examination, RPD—rapidly progressive dementia.

*Grade 1A is a strong recommendation based on high-quality evidence; grade 1B is a strong recommendation based on moderate-quality evidence; grade 2A is a weak or conditional recommendation based on high-quality evidence; grade 2B is a weak or conditional recommendation based on moderate-quality evidence; and grade 2C is a weak or conditional recommendation based on low- or very low-quality evidence.
Nonamnestic forms of AD might include deficits in language, visuospatial abilities, and executive functioning, and diagnosis requires that these deficits occur in at least 2 domains.

Research definitions and criteria, incorporating biomarkers such as CSF levels of amyloid-β\(_{1-42}\), \(\tau\), and hyperphosphorylated \(\tau\), and neuroimaging of cerebral amyloid, were endorsed with the recommendation that they remain within the research arena. The NIA-AA term preclinical AD, referring to cognitively normal individuals with abnormal brain amyloid levels (detected either by positron emission tomography scan or CSF measurement) was rejected as premature.\(^9\) The NIA-AA diagnostic criteria for MCI due to AD was cautiously recommended for use in specialized clinical practice.\(^{10}\) The 2011 American Heart Association–American Stroke Association recommendations for the diagnosis of vascular cognitive impairment were also endorsed.\(^{13}\)

**Neuroimaging.** Although neuroimaging is not required in all persons with cognitive impairment, consistent with previous recommendations, it is indicated in many patients presenting to FPs. Of relevance to FPs is the additional indication for structural neuroimaging: a computed tomography scan or magnetic resonance imaging is indicated in the assessment of a person with cognitive impairment if the presence of unsuspected cerebrovascular disease would change clinical management.

Positron emission tomography metabolic amyloid imaging (using fluoroexyglucose F 18), functional magnetic resonance imaging, and magnetic resonance spectroscopy are intended only for specialized clinical and research settings.

Important for FPs, when faced with results of such investigations obtained outside of Canada, the CCCDDTD4 advised extreme caution with interpretation, as used in isolation these tests cannot diagnose AD or MCI, or differentiate normal from abnormal aging. Consultation with a dementia specialist familiar with the imaging technique is recommended.

**Liquid biomarkers.** The discovery that CSF levels of amyloid-β\(_{1-42}\) are lower in persons with AD has led to numerous measurement studies of this protein in individuals at different stages of dementia. In contrast, CSF levels of \(\tau\) and hyperphosphorylated \(\tau\) are elevated in persons with AD and other neurologic conditions. While these are important developments, the practical message for FPs is that measurement of CSF amyloid-β\(_{1-42}\) and \(\tau\) has no clinical utility in Canada, although it is part of observational and therapeutic research protocols.

**Early-onset dementia.** Dementia that has an onset before the age of 65 years presents unique challenges. Because it is a rare condition, most specialists, other than those with expertise in dementia, will seldom see these patients. In the case of early-onset AD, autosomal-dominant genetic mutations (presenilin 1 and 2, amyloid precursor protein) might be implicated and the issues of genetic counseling and testing are weighty. Onset of symptoms while the person is still in the workforce raises important issues around continued employment, caregiving, insurance, disability benefits, and pensions.

The practical message for FPs is that given the rarity of the condition, all patients with early-onset dementia should be referred to specialists with advanced expertise in this area and with access to genetic counseling and testing if possible. This augments previous recommendations regarding criteria for referral to specialists.\(^{5}\) Family physicians should also be sensitive to the special issues associated with early-onset dementia, particularly regarding loss of employment and access to support services appropriate for that age group.

**Rapidly progressive dementia.** Rapidly progressive dementia is a rare condition with a large number of possible causes. Rapidly progressive dementia has been poorly defined in the literature. Although Creutzfeldt-Jakob disease is a prominent cause (and a mandatory reportable condition in Canada), care must be taken to identify potentially treatable conditions such as unsuspected vascular disease, reversible structural pathogenesis (26% of RPDs), infections, and immunologically mediated disorders.\(^{12}\) Drawing on evidence from case series, a standard definition and an approach to investigation were proposed.

The main message for FPs is that RPD is a condition that develops within 12 months after the appearance of the first cognitive symptoms. Individuals suspected of having RPD should be referred in a timely fashion to physicians who are experienced with RPD, have access to diagnostic facilities, and are able to organize comprehensive diagnostic investigations.

**Symptomatic treatment.** Pharmacologic updates for symptomatic treatment were recommended for AD, Parkinson dementia, depression, agitation, and aggression in AD.

Based on convincing trials showing that cholinesterase inhibitors (ChEIs) have efficacy in conditions other than mild to moderate AD, these drugs should be considered in AD with a component of cerebrovascular disease (the most common type of mixed-pathogenesis dementia), Parkinson dementia, and all stages of AD. These drugs are not recommended for pure vascular dementia (an uncommon condition) or for treating neuropsychiatric symptoms. There is no clear evidence that one ChEI is more efficacious than another, so the choice should be based on other factors. While combination therapy with ChEIs and memantine is rational, based on their different mechanisms of action and safety in combination, there is no clear benefit to this combination. Guidelines are suggested for withdrawal of ChEIs. Adverse events are primarily associated with gastrointestinal side effects, as well as headache and dizziness with memantine\(^{10}\) (Box 3).
Box 3. Symptomatic treatment: Grade 1A is a strong recommendation based on high-quality evidence; grade 1B is a strong recommendation based on moderate-quality evidence; grade 2A is a weak or conditional recommendation based on high-quality evidence; grade 2B is a weak or conditional recommendation based on moderate-quality evidence; and grade 2C is a weak or conditional recommendation based on low- or very low-quality evidence.

Pharmacologic treatment

- Many cases of dementia have more than one condition contributing to causation, most commonly a combination of AD with other brain pathology. Management should be based on those diagnoses that are believed to be the predominant contributing causes (grade 1B).
- ChEIs are recommended as a treatment option for AD with a component of cerebrovascular disease (grade 1B).
- ChEIs are recommended as a treatment option for dementia associated with Parkinson disease (grade 1A).
- All 3 ChEIs have demonstrated efficacy for mild to severe AD. A trial of a ChEI is recommended for most patients with AD (grade 1A).
- There is insufficient and inconsistent evidence on which to make a recommendation either for or against the use of the currently available ChEIs for the treatment of vascular dementia (grade 2B).
- Direct comparisons do not suggest differences between ChEIs (grade 2B). Selection of which agent to use will be based on adverse effect profile, ease of use, familiarity, and differences between the agents in their pharmacokinetics and other mechanisms of action.
- Combination therapy of a ChEI and memantine is rational (as the medications have different mechanisms of action) and appears to be safe, but there is insufficient evidence to recommend for or against this combination (grade 2B).
- Because of increasing central and peripheral cholinergic stimulation, ChEIs might:
  - increase the risk of gastrointestinal bleeding, particularly in patients with ulcer disease or those taking anti-inflammatory drugs;
  - less commonly produce bradycardia or heart block in patients with or without cardiac impairment;
  - exacerbate asthma or other pulmonary disease;
  - cause urinary outflow obstruction;
  - increase risk of seizures; or
  - prolong the effects of succinylcholine (muscle relaxant).
- A trial of antidepressant medications could be considered if the patient has an inadequate response to nonpharmacologic interventions or has a major depressive disorder, severe dysthymia, or severe emotional lability (grade 2A).
- Valproate should not be used for agitation and aggression in AD (grade 1A).
- There is no good evidence to recommend for or against the use of ChEIs or memantine for the treatment of neuropsychiatric symptoms (grade 2B).
- Nonpharmacologic interventions for agitation and aggression in dementia include recognition and management of potentiating factors (medical, psychiatric, medications, environmental).
- Risperidone, olanzapine, and aripiprazole should be considered for severe agitation, aggression, and psychosis associated with dementia where there is risk of harm to the patient or others. The potential benefit of all antipsychotic medications must be weighed against the substantial risks such as cerebrovascular adverse events and mortality (grade 2A).
- Currently, there is insufficient evidence to recommend for or against the use of quetiapine in the management of severe agitation, aggression, and psychosis associated with dementia (grade 2B).
- There is insufficient evidence to recommend for or against the use of selective serotonin reuptake inhibitors or trazodone in the management of agitated patients (grade 2B).

Discontinuation of ChEIs

- Because of known side effects and drug costs of continuing therapy, discontinuation of ChEIs should be considered and balanced against possible worsening of cognitive function and greater functional impairment (grade 2B). It is suggested that ChEIs be discontinued when the following are relevant:
  - The patient, caregiver, or substitute decision maker decide to stop ChEIs after being apprised of the risks and benefits of continuation and discontinuation.
  - The patient is nonadherent and continued prescribing would be useless.
  - The patient’s rate of cognitive, functional, or behavioural decline is greater on treatment compared with that before being treated.
  - The patient experiences intolerable side effects that are definitely or probably related to the ChEI.
  - The comorbidities of the patient make continued use of the agent unacceptably risky or futile (eg, terminal illness).
  - The patient’s dementia progresses to a stage (eg, Global Deterioration Scale stage 7) where there would be no meaningful benefit from continued therapy.
- It is suggested that the dose be tapered before stopping the agent. If discontinued because of perceived lack of effectiveness, it is recommended that the patient be monitored over the next 1-3 mo for evidence of an observable decline. If this occurs, it is suggested that reinstating therapy be considered (grade 2C).

AD—Alzheimer disease, ChEI—cholinesterase inhibitor.
Nonpharmacologic treatments should be considered before drug therapy in people with dementia who have agitation or aggression, as potential benefit of all antipsychotic medications must be weighed against their substantial risks (cerebrovascular accidents and mortality). Risperidone, olanzapine, and aripiprazole should be considered for severe agitation, aggression, and psychosis with dementia, where there is risk of harm to the patient or others. The roles of selective serotonin reuptake inhibitors, trazodone, and quetiapine are unclear in the management of agitation.

Valproate should not be used for agitation and aggression in patients with AD. New information regarding toxicity, accelerated brain volume loss, greater cognitive impairment, and similar risk of mortality found with antipsychotic medications in dementia patients has resulted in a strong recommendation against the use of valproate in this context.

Future guideline development. For guideline updates to remain relevant, FPs should contribute to all stages of development, including topic selection. Future topics should address challenges of delivering front-line, comprehensive, and holistic care for families, caregivers, and patients living with dementia. Such topics might include strategies for disclosing a new dementia diagnosis, an approach to dementia in the context of multiple comorbidities, management of responsive behaviour in the community, assessing and supporting caregivers, an approach to younger children and adolescents living with adults with dementia, sex and dementia, and primary care interprofessional programs for dementia.

Conclusion

Several CCCDTD4 recommendations are relevant to FPs, including updates on symptomatic treatment of dementia and guidelines for managing patients with early-onset dementia and RPD. Despite notable technologic advances, diagnosis remains fundamentally clinical. However, it is critical for FPs to be aware of such advancing technologies that are rapidly changing how dementia is conceptualized and discussed in Canada and elsewhere. At CCCDTD4, we aimed to address several barriers to optimal use of dementia guidelines, recognizing FPs are key stakeholders in the delivery of dementia care.

Dr Moore is Associate Professor in the Department of Family Medicine at McMaster University in Hamilton, Ont. Dr Patterson is Professor in the Division of Geriatric Medicine of the Department of Medicine at McMaster University. Dr Lee is Associate Clinical Professor in the Department of Family Medicine at McMaster University. Dr Vedel is Assistant Professor in the Division of Geriatrics of the Department of Family Medicine at McGill University in Montreal, Que. Dr Bergman is Chair of the Department of Family Medicine, Professor of Family Medicine in the Department of Medicine and Oncology, and Dr Joseph Kauffmann Professor of Geriatric Medicine at McGill University.

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Contributors

Dr Moore, Dr Lee, Dr Vedel, and Dr Bergman participated in the conference as representatives of family medicine. Dr Patterson oversaw the conference as chair. All authors contributed to preparing recommendations, preparing the manuscript for submission, and providing final approval for publication. This article is submitted on behalf of participants of the Fourth Canadian Consensus Conference on the Diagnosis and Treatment of Dementia: A. Al Rashed, R. Bartha, H. Bergman, J. Bethell, S. Black, C. Bocti, M. Borrie, A. Burnham, C. Cook, J. Crowson, M. Donnelly, H. Feldman, S. Gauthier, M. Gordon, G. Heckman, N. Herman, D. Hogan, G.Y.R. Hsiung, G. Inglis, C. Jacova, R. Laforce, K. Lancot, K. Leclaire, L. Lee, M. Masselis, F. Massoud, A. Moore, C. Patterson, S. Prasad, K. Rabheru, K. Rockwood, P. Rosa-Neto, D. Sadovnick, J.P. Soucy, L. Trudeau, I. Vedel, M. Williams.

Competing interests

None declared.

Correspondence

Dr Ainsley Moore, Department of Family Medicine, McMaster University, 1200 Main St W, Hamilton, ON L8N 3Z5; telephone 905 525-9140; fax 905 521-5594; e-mail amoore@mcmaster.ca

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