Recommendations of the 4th Canadian Consensus Conference on the Diagnosis and Treatment of Dementia (CCCDTD4)

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ABSTRACT

The 4th CCCDTD convened in May 2012 in Montreal with the primary aim of updating the previous diagnostic approach to AD, taking into account the revised diagnostic criteria proposed by the International Working Group (IWG) and the recommendations made by the National Institute on Aging—Alzheimer Association workgroups.

Key words: consensus, dementia, Alzheimer, diagnosis, imaging, symptomatic treatments

INTRODUCTION

Since 1989, three Canadian Consensus Conferences on the Diagnosis and Treatment of Dementia (CCCDTD)[1,2,3] have led to evidence-based recommendations on the diagnosis and treatment of Alzheimer's disease (AD) and related dementias. Previous CCCCDTDs have attempted to make recommendations relevant to health professionals of all disciplines treating dementia (e.g., primary care practitioners, as well as neurologists, geriatricians, and psychiatrists). Recommendations have been published in medical journals reaching out to a wide readership (such as the *Canadian Medical Association Journal* (CMAJ), as well as more specialized readership (such as the *Canadian Journal of Neurological Sciences* and *Alzheimer's & Dementia*). Following the last CCCDTD in 2006, the CMAJ published a series of case-based articles with recommendations for each stage of AD (asymptomatic at risk,[4] mild cognitive impairment,[5] mild to moderate dementia,[6,7] and severe dementia[8]).

The 4th CCCDTD convened in May 2012 in Montreal with the primary aim of updating the previous diagnostic approach to AD,[9] taking into account the revised diagnostic criteria proposed by the International Working Group (IWG)[10,11] and the recommendations made by the National Institute on Aging—Alzheimer Association workgroups (NIA/AA)[12,13,14] to which a Canadian perspective has already been published.[15]

METHODS

The methodology of the meeting can be summarized as follows: The process was guided by the tenets of the AGREE collaboration to which 20 of the 23 criteria were met.[16] While previous CCCDTDs had used the evidence grading system developed by the Canadian Task Force on Preventive Health Care, for this iteration we attempted to follow, where possible, the GRADE system, in keeping with current recommendations for the conduct of consensus conferences.[17]

Complete background articles written by workgroups were posted to a password-protected website, accessible to all conference participants, who were encouraged to post comments. The recommendations, modified where appropriate as a result of participants' comments, were then posted for online voting. Organizations relevant to the care of people with dementia were approached to appoint delegates. These delegates had full access to the background articles, were encouraged to comment, and were allowed to vote on recommendations. Online voting was closed one day before the conference assembly, which was held in Montréal on May 4th and 5th, 2012. At the conference, each topic was briefly reviewed before voting was carried out on each recommendation. All participants (except for the four industry observers) were permitted to vote. In the event of failed consensus, online votes of conference participants who were not able to attend the assembly were taken into account. As in each previous consensus conference, consensus was defined as 80% or more of conference participants voting

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for the recommendation. Partial consensus was defined as 60–79% of votes. Recommendations reaching consensus (≥ 80%) are listed in the tables of this article. Recommendations reaching only partial or no consensus are commented upon in the text. Strength of evidence is listed in the tables where possible. Recommendations clearly applicable only for research are flagged with "R" in the tables.

Most of the recommendations are particularly relevant to specialists treating patients with dementia because of the nature of the topics discussed: definitions/new diagnostic criteria for AD, use of neuroimaging and of liquid biomarkers, early onset dementia, and rapidly progressive dementia. Recommendations for these topics are therefore presented in this joint publication in key specialty journals in Canada: the *Canadian Journal of Neurological Sciences* and the *Canadian Journal of Geriatrics*. Symptomatic treatments, which are relevant to all treating physicians, are also reported in this article.

Definitions/New Diagnostic Criteria

The motivation to revise criteria in Canada was the evolution of thinking about how dementia might be approached in light of new criteria in the United States. A proposal was made by the IWG led by Bruno Dubois and Howard Feldman to diagnose AD even before dementia has become manifest, using a specific clinical phenotype (memory impairment of the hippocampal type) and a biomarker.[10] In 2011, three workgroups of the NIA/AA recommended criteria for the diagnosis of dementia caused by AD,[12] MCI due to AD,[13] and asymptomatic AD.[14] These workgroups have embraced the Dubois/Feldman proposal in its reliance on biomarkers. In additional, the statement about vascular contributions to cognitive impairment (VCI) and dementia made by the American Heart Association/American Academy of Neurology[18] was also examined. Against this background, the CCCDTD4 recommendations are listed in Table 1.

The practical messages are: (1) a recommendation in favor of the criteria for MCI due to AD, but to be used cautiously and only in specialized clinical practice; (2) a strong recommendation against the diagnosis of "prodromal AD" outside a research setting; (3) the recognition of the fact that an at-risk state for AD in asymptomatic persons should be made only in a research setting; and (4) the measurement of brain amyloid deposition using PET imaging in asymptomatic persons should be performed only in a research setting

Early Onset Dementia

In the context of an international effort to treat people who carry mutations for genes causing early onset familial AD,[19] and the requests for memory consultations for people in midlife, the issue of early onset dementia (i.e., prior to age 65) was examined. The recommendations outlined in Table 2 were approved by consensus of ≥ 80%.

TABLE 1.
Recommendations regarding definitions of dementia, AD, and VCI

- We recommend the adoption of the criteria for dementia proposed by the NIA/AA working group in 2011.
- We recommend the adoption of the criteria concerning probable and possible Alzheimer's Disease dementia proposed by the NIA/AA working group in 2011.
- We recommend the adoption of the criteria for MCI due to AD proposed by the NIA-AA working group in 2011.
- We recommend reassessment of the utility of the concept of prodromal AD in the future when biomarkers are available, validated, and ready for use in Canada.
- We recommend the IWG definition of asymptomatic at-risk for AD only for research purposes.
- Given that the presence of brain amyloid in normal people is of uncertain significance, we discourage the use of amyloid imaging in individuals without memory loss, outside of the research setting. The medical community should be clear in its discussions with patients, the media, and the general population that the presence of brain amyloid in normal people is of unclear significance at the present time.
- We recommend the 2011 ASA/AHA recommendations for the diagnosis of VCI.

TABLE 2.
Recommendations regarding early onset dementia

- All patients with early onset dementia should be referred to a memory clinic, preferably one with access to genetic counselling and testing when appropriate.
- The cost of genetic counselling and testing should be covered by public funding.
- 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.
- Considering the rarity of early onset dementia, a national registry for interested at-risk individuals, mutation carriers and symptomatic patients will facilitate therapeutic research.
- This registry should be supported by public funding.

The practical message is that patients with dementia starting before age 65 should be referred to a specialist, preferably in a clinical setting where genetic counselling and testing is available. The CCCDTD had recommended in 1999 that all such patients be referred to a specialist. The current CCCDTD recommends that even among specialists, referral should be made to colleagues with special expertise in this area.

Rapidly Progressive Dementia

In the context of increasing awareness of the many causes of rapidly progressive dementia (RPD), particularly

Creutzfeldt-Jakob Disease, a mandatory reportable condition in Canada, the CCCDTD felt the need to define this condition operationally and suggested appropriate referral. Furthermore the common occurrence of rapid clinical decline in later onset dementia such as AD deserved a recommendation. The recommendations listed in Table 3 were approved unanimously.

The practical messages are: (1) patients with RPD where the diagnosis remains uncertain should be referred rapidly to appropriate specialty settings; and (2) patients with known AD who demonstrate faster-than-expected clinical decline should be reassessed for co-morbid conditions.

Neuroimaging

Neuroimaging was the most complex topic in this round of CCCDTD discussions. Reflecting the many technical advances in this area, the topic was operationally divided into an introduction with general recommendations, structural neuroimaging (CT and MRI), functional MRI, PET imaging (discussing both ^{18}FDG and amyloid-binding ligands imaging), SPECT cerebral blood flow studies and MRI spectroscopy. Many of the recommendations are research related, since few of these tests are universally available for clinical implementation at this time. The issue of whether all patients with dementia should have structural imaging is debated at every CCCDTD conference, with the opinion that it is not required in all patients, but rather for those who have special clinical features (Table 4 from Patterson et al.[2]). One participant suggested that the age of 60 in that list was arbitrary and should be deleted. Participants voted against the recommendation that at least one structural imaging procedure should be done to establish the presence of clinically unsuspected cerebrovascular disease and to rule out potentially reversible structural etiologies in persons with cognitive impairment (26%). The recommendation that Health Canada approve the use of PET amyloid imaging in tertiary care dementia clinics did not reach consensus (63%). There was only partial consensus for the proposition that for a patient with MCI evaluated by a dementia specialist and in whom clinical management would be influenced by evidence of an underlying neurodegenerative process, an ^{18}F-FDG PET scan be performed or, if not available, then a SPECT rCBF study be performed (72%) (see Tables 4 to 10).

The practical message is that structural imaging is not required in all (although will be indicated in most) persons with cognitive impairment. Although more costly and less available, MRI is preferable to CT. Where available, PET-^{18}FDG and/or PET amyloid imaging can be used for clinical purpose in patients with atypical dementias.

TABLE 3.
Recommendations regarding rapidly progressive dementia

- It is suggested that RPD be defined as a dementia which develops within 12 months after the appearance of first cognitive symptoms (Grade 2C).
- It is suggested that individuals suspected of RPD be referred to physicians who are experienced and have access to the diagnostic facilities able to mount an organized and comprehensive diagnostic procedure (Grade 2C).
- After exclusion of delirium and evident underlying causes of RPD, it is suggested that a diagnostic strategy for RPD be based of the prevalence of causes of RPD in case series (Grade 2B).
- The diagnostic strategy should emphasize the detection of potentially curable conditions, such as infections, immune mediated and toxic metabolic causes (Grade 2B).
- 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 co-morbid conditions and review pharmacological management (Grade 2B).

TABLE 4.
Recommendations from CCCDTD2 about CT scan needed if:

- age less than 60 years
- rapid (e.g., 1 or 2 months) unexplained decline in cognition or function
- "short" duration of dementia (less than 2 years)
- recent and significant head trauma
- unexplained neurological symptoms (e.g. new onset of severe headache or seizures)
- history of cancer (especially in sites and types that metastasize to the brain)
- use of anticoagulants or history of bleeding disorder
- history of urinary incontinence and gait disorder early in the course of dementia (as may be found in normal pressure hydrocephalus)
- any new localizing sign (e.g., hemiparesis or a Babinski reflex)
- unusual or atypical cognitive symptoms or presentation (e.g. progressive aphasia)
- gait disturbance

TABLE 5.
Recommendations about FDG-PET and SPECT rCBF imaging

- For a patient with a diagnosis of dementia who has undergone the recommended baseline clinical and structural brain imaging evaluation and who has been evaluated by a dementia specialist but whose underlying pathological process is still unclear, preventing adequate clinical management, we recommend that the specialist obtain a 18F-FDG PET scan for differential diagnosis purposes (Grade 1B).
- If such a patient cannot be practically referred for a –FDG-PET scan, we recommend that a SPECT rCBF study be performed for differential diagnosis purposes (Grade 2C).

TABLE 6.
Recommendations regarding structural imaging, CT, and MRI

- We recommend a head MRI when a radiologist/neuroradiologist and/or a cognitive specialist (neurologist, geriatrician, or geriatric psychiatrist) can interpret patterns of atrophy and other features that may provide added diagnostic and predictive value as deemed appropriate by the specialist (Grade 2B).
- Standardization of clinical acquisition of core MRI dementia sequences is recommended in Canadian Centers that have radiologists and cognitive specialists with expertise in assessing cognitive disorders, particularly when repeat MRI images can provide additional diagnostic, prognostic and safety information (Grade 2B).
- In addition to previously listed indications for structural imaging, a CT or MRI should be undertaken in the assessment of a person with cognitive impairment if the presence of unsuspected cerebrovascular disease would change the clinical management.
- When available in the clinic, we recommend that cognition specialists use the computer images of the brain to educate persons with cognitive impairment about changes in the brain. This knowledge may reinforce adherence to vascular risk factors management and to life style modifications to improve brain health (Grade 3C).

TABLE 7.
Recommendations regarding functional MRI

- We recommend against the use of fMRI for the clinical investigation of patients presenting with cognitive complaint (Grade 1B).
- Future studies should use standardized acquisition of images protocol and experimental paradigm to allow pooling of data (Grade 1C;R).
- Future studies with large number of participants and longer period of follow-up are needed to allow firm conclusions on the value of fMRI in early detection of dementia and on predicting conversion of MCI to AD (Grade 1B; R).
- Future studies with large number of participants and longer period of follow-up are needed to allow firm conclusions regarding the value of fMRI in distinguishing between AD and non-AD dementia such as FTD and LBD (Grade 1B; R).
- Future studies with large number of participants and longer period of follow-up are needed to allow firm conclusions on the value of fMRI in assessing changes in brain activation in response to intervention such as cognitive training and pharmacotherapy (Grade 1C; R).
- Future studies with large number of participants and longer period of follow-up are needed to allow firm conclusions on the value of fMRI mapping brain activation in various neuropsychiatric and behavioral symptoms in the context of preclinical and clinical dementia such as depression, apathy and psychosis, which will help in developing specific treatments for these symptoms (Grade 2C).

TABLE 8.
Recommendations regarding PET amyloid imaging

- Although amyloid imaging represents a promising technique in the evaluation of dementia, there are many unknowns that could impact on its diagnostic utility and therefore we recommend that its use be restricted to research at present (Level 1C; R).
- Amyloid imaging is not currently approved in Canada. Should amyloid imaging become available to Canadian clinicians in the future, it must not be considered a routine test and we recommend it is regarded as an adjunct to a comprehensive evaluation for complex atypical presentations in referral to tertiary care Memory Clinics when a more accurate clinical diagnosis is needed (Grade 1B).
- Should this technique become available to Canadian clinicians in the future, we recommend against its use in cognitively normal individuals or for the initial investigation of cognitive complaints (Grade 1B).
- When faced with amyloid test results obtained outside Canada, physicians should be very cautious in their interpretation, i.e. used in isolation this test cannot diagnose AD, MCI, or differentiate normal from abnormal aging, and we recommend they consult with a dementia specialist familiar with this technique.
- At present, there is no clinical indication for amyloid imaging in cognitively normal individuals, initial investigation of cognitive complaints, differentiating AD from other Aβ -associated dementia (e.g. DLB, CAA), differentiating between AD clinical variants (e.g., classic amnestic AD vs. PCA or lvPPA), and differentiating between non-AD causes of dementia (e.g., molecular subtypes of FTLD).
- In research settings with amyloid imaging capabilities, investigators should be encouraged to develop projects that further validate the clinical and research uses of this technique and evaluate it readiness for translation to clinical care (R).
- Trial designers are strongly encouraged to use this technique to: (1) decrease the heterogeneity of their MCI population; (2) identify a cohort that is likely to respond to a drug with anti-amyloid properties; and (3) study patients that are likely to convert to AD in a relatively short time frame (R).
- Testing and longitudinal follow-up of asymptomatic individuals or patients with subjective cognitive impairments not meeting MCI criteria, or at-risk individuals (e.g., gene mutation carriers, family history of AD, ApoE ε4) should be restricted to research (R).
- Future research should explore (1) the natural evolution of amyloid burden and its role in the pathophysiology of AD and other dementias, (2) its use as a potential surrogate marker for anti-amyloid therapies, (3) the value of new 18F amyloid tracers, and should (4) perform PET pathology correlations, and (5) compare amyloid imaging with CSF AD biomarkers as well as downstream markers of degeneration (R).

Liquid Biomarkers (see Table 11)

In the context that cerebrospinal fluid (CSF) examination for Aβ42 and tau levels is a component of the biomarkers for AD in the IWG and the NIA/AA criteria, it was important to evaluate the feasibility and validity of CSF examination for routine diagnostic purpose or in atypical cases. Although everyone agreed that plasma Aβ42 are not reliable and are not recommended for clinical practice, the proposal that CSF Aβ42 and tau levels be measured did not reach consensus (64%), nor did the proposal that measures of CSF Aβ1-42, total tau and phosphorylated tau at ser 181 should be collected following a specific protocol and the quantification must be carried out by an experienced lab with a validated technology and continuous participation in quality control programs (71%).

The practical message is that, for now, measurement of CSF Aβ1-42 and tau have no clinical utility in Canada, although they are part of research protocols in observational and therapeutic studies.

Update on Symptomatic Treatments

Although there have been no new drugs approved in Canada or elsewhere since the CCCDTD3 meeting in 2006, it was considered important to review new evidence on the indications and best use of these drugs (Tables 12 and 13). Special emphasis was placed on discontinuation rules for cholinesterase inhibitors (CIs) which have not previously been clearly defined in the literature.

The practical messages are that: (1) concurrent causes of dementia have to be managed; (2) CIs are recommended for AD in mild to severe stages of dementia, AD with a cerebrovascular component, Parkinson Disease dementia, but not for probable vascular dementia; (3) the combination of CIs and memantine is logical, but an additive benefit has not been conclusively demonstrated; (4) for severe agitation the atypical antipsychotics risperidone, olanzapine and aripiprazole are recommended, but risks of therapy must be carefully weighed against potential benefits; (5) there is insufficient evidence for or against CIs, memantine, SSRIs, or trazodone as first-line therapy for neuropsychiatric symptoms; and (6) valproate should not be used for agitation and aggression.

TABLE 9
Recommendations regarding MR spectroscopy

- Magnetic resonance spectroscopy shows promise for predicting which people with mild cognitive impairment are likely to progress to dementia. However, it is not currently recommended for clinical use to make or differentiate a diagnosis of dementia in people presenting with mild cognitive impairment (Grade 2C; R).
- 1H MRS remains a promising technique for the identification of subjects with mild cognitive impairment who will convert to dementia. Further multi-site longitudinal studies should be conducted to establish normative values. Such studies should utilize standardized enrollment criteria, diagnosis criteria, data acquisition methods, and include automated analysis of spectra that incorporates proper prior knowledge of metabolite lineshapes (R).
- Standardized 1H MRS data acquisition and analysis methods should be developed in co-ordination with recommendations from the International Society of Magnetic Resonance in Medicine (R).
- Future 1H MRS studies to demonstrate clinical effectiveness should utilize 3 Tesla MRI where available to increase data quality (R).

TABLE 10.
Recommendations regarding other neuroimaging modalities

- Imaging biomarkers of neuro-inflammation or tau pathology in dementia patients are not recommended in clinical practice.
- Although there is a growing body of literature supporting the use of dopamine presynaptic imaging agents for differentiating Lewy Body from AD disease, these imaging agents are not yet recommendable for clinical practice.

TABLE 11.
Recommendations regarding liquid biomarkers

- Plasma Aβ1–42 levels are not recommended for clinical practice.

CONCLUSION

Despite a large number of important advances, the CCCDTD4 concluded that fundamental changes in dementia diagnosis and management have not yet arrived. The IWG and NIA/AA AD criteria chiefly serve to codify standard practice in specialty settings for dementia and MCI due to AD, and for research at all stages of AD. As result, Canadian physicians who are not dementia experts will be little affected by the CCCDTD4 recommendations. The 1999 consensus recommended that younger patients (those < 65 years) and patients with rapidly progressive dementia be referred to dementia specialists and this has not changed, except that even among specialists in the disciplines to which such patients might be referred, tertiary referral of such patients should be made to colleagues with special expertise for that age group.

If the use of biomarkers becomes justified by further evidence, this will have implications for how cognitive decline is evaluated, and likely will have very substantial economic implications. Even now, Canadian physicians engaged in dementia research will need to consider how the new research criteria will impact their access to imaging modalities and laboratory tests that are not yet standard for dementia care in Canada.

TABLE 12.
Recommendations regarding symptomatic treatments

- Many cases of dementia have more than one condition contributing to causation. Most commonly this will be a combination of Alzheimer's disease with other brain pathology. We recommend that management be based on those diagnoses that are believed to be the predominant contributing cause(s) (Grade 1B).
- We recommend cholinesterase inhibitors as a treatment option for Alzheimer's disease with cerebrovascular disease (Grade 1B).
- We recommend cholinesterase inhibitors as a treatment option for dementia associated with Parkinson's disease (Grade 1A).
- There is insufficient and inconsistent evidence on which to make a recommendation either for or against the use of the currently available cholinesterase inhibitors for the treatment of vascular dementia (Grade 2B).
- All three cholinesterase inhibitors have demonstrated efficacy for mild to severe AD. We recommend a trial of a cholinesterase inhibitor for most patients with AD (Grade 1A).
- Direct comparisons do not suggest differences between cholinesterase inhibitors (Grade 2B). Selection of which agent to be used 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 cholinesterase inhibitor 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).
- If the patient had an inadequate response to the non-pharmacological interventions or has a Major Depressive Disorder, severe dysthymia, or severe emotional liability, we recommend that a trial of an antidepressant could be considered (Grade 2A).
- Based on good evidence we recommend that 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 cholinesterase inhibitors and/or memantine for the treatment of neuropsychiatric symptoms as a primary indication (Grade 2B).
- We recommend that risperidone, olanzapine and aripiprazole be used for severe agitation, aggression and psychosis associated with dementia where there is risk of harm to the patient and/or others. The potential benefit of all antipsychotics must be weighed against the significant risks such as cerebrovascular adverse events and mortality (Grade 2A).
- 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 SSRIs or trazodone in the management of agitated patients (Grade 2B).

TABLE 13.
Recommendations regarding discontinuation of cholinesterase inhibitors

- Discontinuing cholinesterase inhibitors in patients with moderate to severe Alzheimer's disease may lead to worsening of cognitive function and greater functional impairment as compared to continued therapy (Grade 2B). This must be balanced with the risk for known side-effects and drug costs if therapy continues. It is suggested that cholinesterase inhibitors be discontinued when:
  a) The patient and/or their proxy decision-maker decide to stop after being appraised of the risks and benefits of continuation and discontinuation;
  b) The patient is sufficiently non-adherent with the medication that continued prescription of it would be useless, and it is not possible to establish a system for the administration of the medication to rectify the problem;
  c) The patient's rate of cognitive, functional, and/or behavioural decline is greater on treatment compared to that prior to being treated;
  d) The patient experiences intolerable side effects that are definitely or probably related to the cholinesterase inhibitor;
  e) The comorbidities of the patient make continued use of the agent either unacceptably risky or futile (e.g., terminally ill);
  f) The patient's dementia progresses to a stage (e.g., Global Deterioration Scale stage 7) where there would be no clinically meaningful benefit from continued therapy.
- When a decision has been made to discontinue therapy because of a perceived lack of effectiveness, it is suggested that the dose be tapered before stopping the agent and that the patient be monitored over the next 1-3 months for evidence of an observable decline. If this occurs, it is suggested that consideration be given to reinstating therapy (Grade 2C).

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CONFLICT OF INTEREST DISCLOSURES

The authors declare that no conflicts of interest exist.

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