Part 2: Early detection, assessment and treatment in relation to the new guidelines

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Disclosure: Relationships with commercial interests

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- **Speakers bureaux, honoraria: Alzheimer's Society, Dementia Alliance**
- **Consulting fees: Nil**
- **Other: Secretarial support from Hamilton Health Sciences**
- **Potential for conflict of interest: Nil**
- **Potential for bias: Nil**

Why did we need another CCCDTD?

- New definitions and conceptualization of AD
- Availability of biomarkers (CSF, amyloid and functional MRI neuroimaging)
- Ethical concerns about clinical use (misuse) of biomarkers
- Some important therapeutic updates
- Target audience: non dementologist specialists, FMDs

3rd Canadian Consensus Conference
on Diagnosis and Treatment of Dementia

March 9-11, 2006
Hotel Delta President Kennedy
Montreal, Quebec

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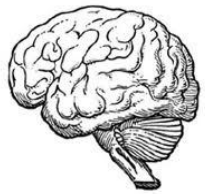
- Building upon 1989 & 1999 cccd
- Posting background papers to website
- Comments added on line
- Voting online
- Advanced dissemination strategy (specific $) CMAJ, Alzheimer's & Dementia



Montréal, May 4-5

2012

- Adherence to AGREE template (21/22 criteria)
- Use of GRADE evidence classification
- Ethics consultant and consumer involvement
- Advanced knowledge translation strategy **(DKTN, publications, web based)**
- No industry funding

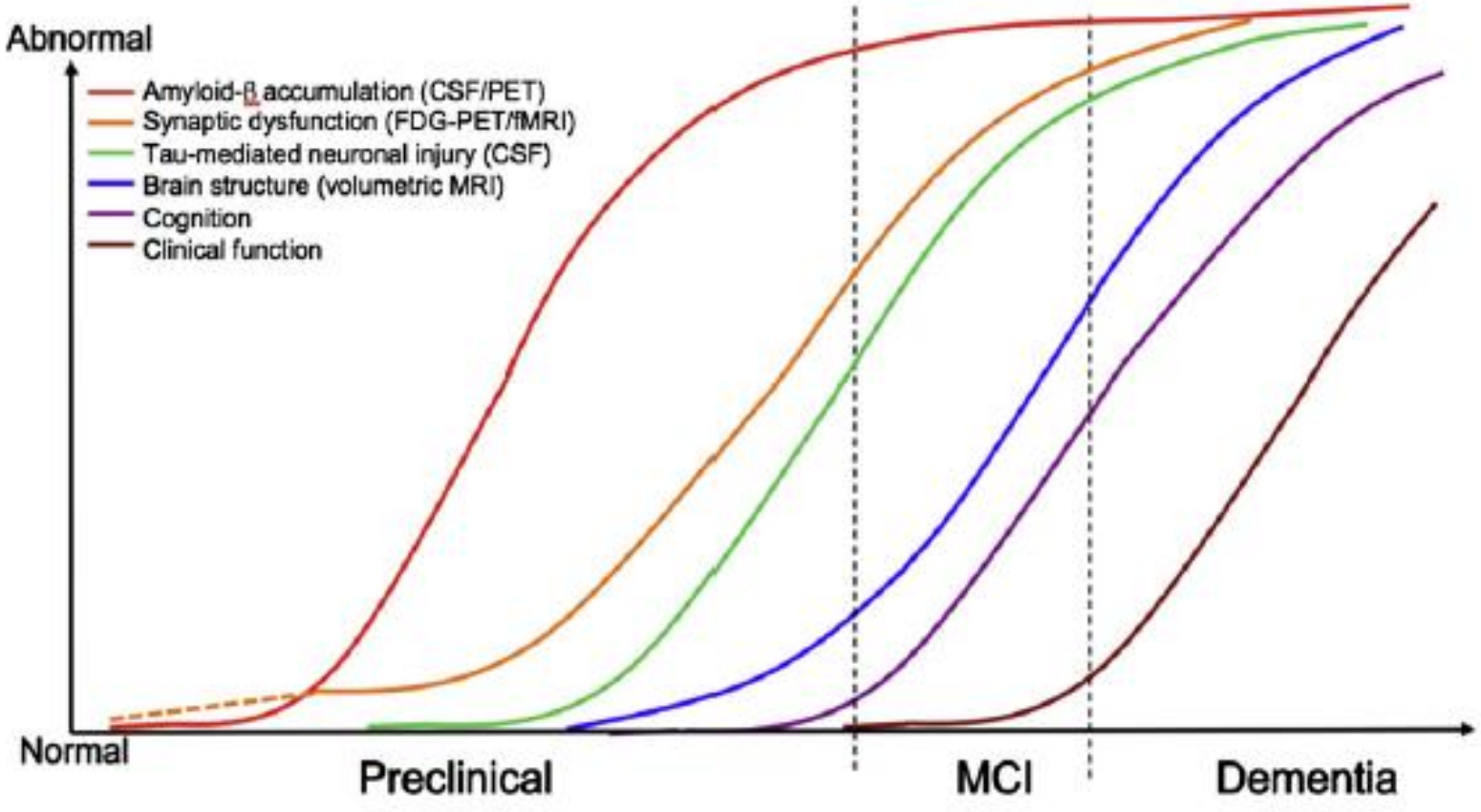
Steering Committee

- Christopher Patterson (Co-Chair)
- Serge Gauthier (Co-Chair)
- Howard Chertkow
- Michael Gordon (Ethics consultant)
- Pedro Rosa-Neto
- Ken Rockwood (CDKTN)
- Jean-Paul Soucy

cccdtd4 addressed the following topics:

- Definitions
- Neuroimaging (clinical and research recommendations)
- Liquid biomarkers
- Early onset dementia
- Rapidly progressive dementia
- Pharmacology update
- Knowledge translation

Theoretical changes of biomarkers in AD



Sperling R et al Alz Dement 2011; 7: 280

A new lexicon of Alzheimer's Disease (IWG)

	AD diagnosis	Presence of impairment on specified memory tests	Evidence of biomarkers in vivo	Additional requirements
Typical AD	Yes	Required	Required	None
Atypical AD	Yes	Not required	Required	Specific clinical presentation
Prodromal AD	Yes	Required	Required	Absence of dementia
AD dementia	Yes	Required	Required	Presence of dementia
Mixed AD	Yes	Required	Required	Evidence of comorbid disorders
Preclinical AD				
Asymptomatic at risk for AD	No	Not present	Required	Absence of symptoms of AD
Presymptomatic AD	No	Not present	Not required	Absence of symptoms of AD and presence of monogenic AD mutation
Mild cognitive impairment	No	Not required	Not required	Absence of symptoms or biomarkers specific for AD

AD=Alzheimer's disease.

Table 2: Comparative features of the different conditions described in the new lexicon according to the new research criteria framework[6]

Dubois B et al. Lancet Neurol 2010; 9: 1118

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Definitions

	For
We recommend the adoption of the 2011 NIA-AA criteria proposed by the working group for:	
Dementia	**All**
Probable and possible AD	**All**
Core clinical criteria for MCI	**All**
We recommend the 2011 ASA/AHA recommendations for the diagnosis of VCI	**All**

Dementia (NIA-AA)

is diagnosed when there are cognitive or behavioural symptoms which:

1. Interfere with function at work or usual activities
2. Represent a decline from previous function
3. Are not explained by delirium or major psychiatric disorder
4. Cognitive impairment is detected by:
   (a) history (person and knowledgeable informant)
   (b) mental status or bedside neuropsychological testing

5. The cognitive or behavioural impairment involves a minimum of 2 of the following domains

(a) memory

(b) reasoning, handling complex tasks, judgment

(c) impaired visuospatial function

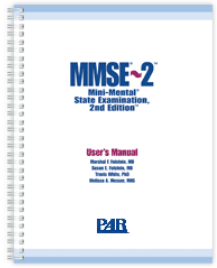
(d) language

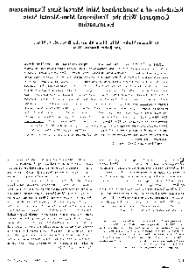
(e) changes in personality behaviour or comportment

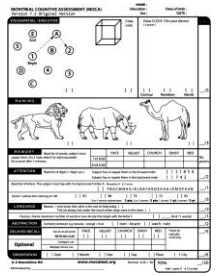
McKhann G et al. Alzheimer's and Dementia 2011; 7: 263

Note that:

- Dementia is a clinical diagnosis
- Loss of function is central
- Memory loss is not an essential feature
- Cognitive scores are an addition to, and not a replacement for complete assessment







Alzheimer's disease (probable) NIA-AA

- Dementia
- Insidious onset
- Clear cut history of worsening
- Initial and prominent cognitive deficits on history and examination in one of:

(a) amnestic presentation

(b) non amnestic presentation

language (PNFA)

visuospatial (PCA)

executive

Not probable AD if:

- Substantial evidence of cerebrovascular disease
- Core features of LBD
- Prominent features of Behavioural variant FTD
- Prominent features of semantic dementia or PPA
- Other neurological or non neurological illness or drugs

McKhann G et al Alz Dement 2011; 7: 263

Vascular Cognitive Impairment: Probable VaD (NIA-AA)

- Dementia
- The deficits in ADL are independent of the motor/sensory sequelae of the vascular event.
- There is no history of gradually progressive cognitive deficits before or after the stroke that suggests the presence of a nonvascular neurodegenerative disorder.

Gorelick P et al. Stroke 2011; 42: 2672

Vascular Cognitive Impairment: Probable VaD (NIA-AA)

- There is cognitive impairment and imaging evidence of cerebrovascular disease and
- (a) There is a clear temporal relationship between a vascular event (e.g. clinical stroke) and onset of cognitive deficits, or
- (b) There is a clear relationship in the severity and pattern of cognitive impairment and the presence of diffuse, subcortical cerebrovascular disease pathology (e.g. as in CADASIL).

Gorelick P et al. Stroke 2011; 42: 2672

cccdtd4 did not address:

- **DLB** (Parkinsonism, fluctuation, hallucinations, REM sleep disorder, neuroleptic sensitivity)
- **FTD** (behaviour-disinhibition, apathy, loss of insight and judgement; language-progessive expressive aphasia)
- **NPH** (triad of gait apraxia, incontinence, cognitive deficits)

Definitions

Research recommendation:

For

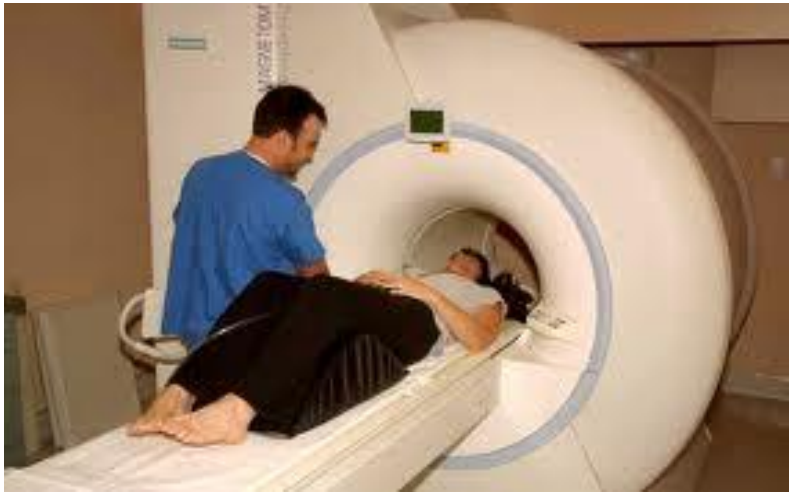
We recommend the IWG definition of "asymptomatic at-risk for AD" states for **research purpose**.

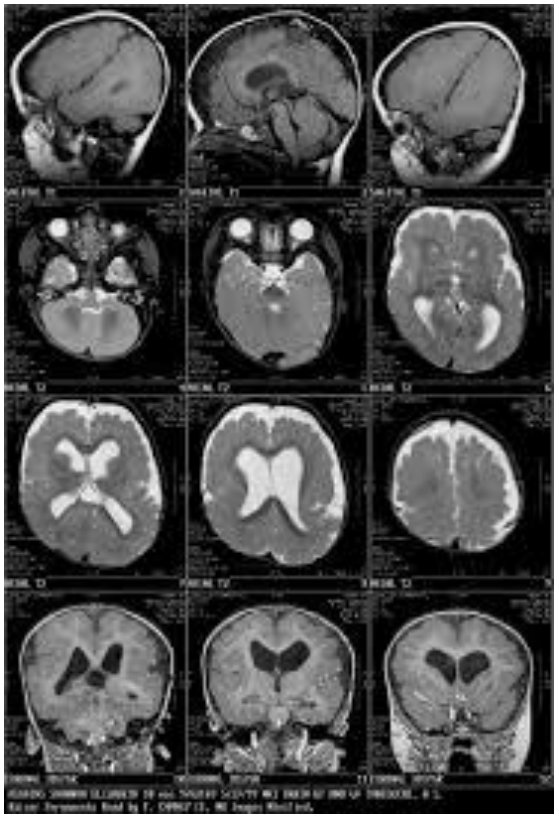
All

We recommend **reassessment** of the utility of the concept of prodromal AD in the future when AD-PP biomarkers are available, validated, and ready for use in Canada.

All

Neuroimaging

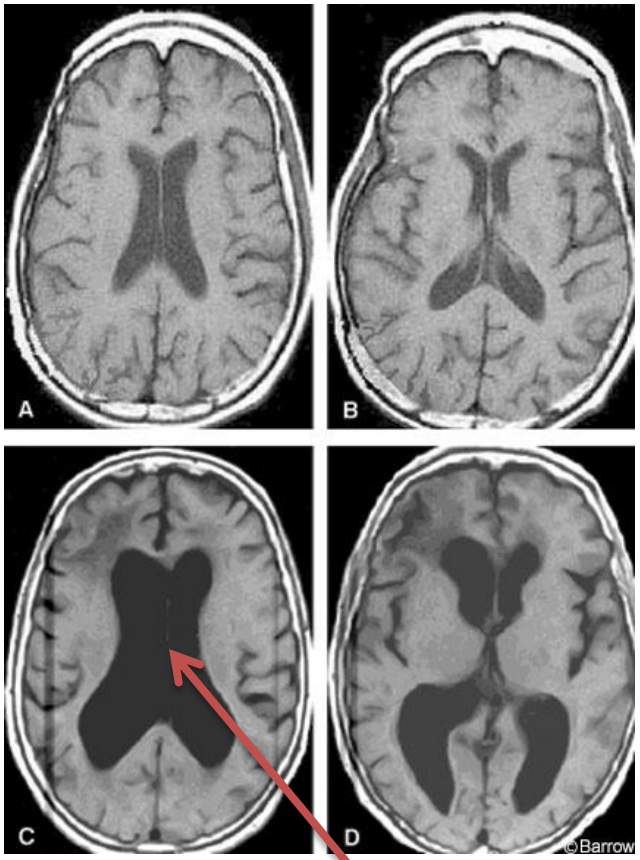




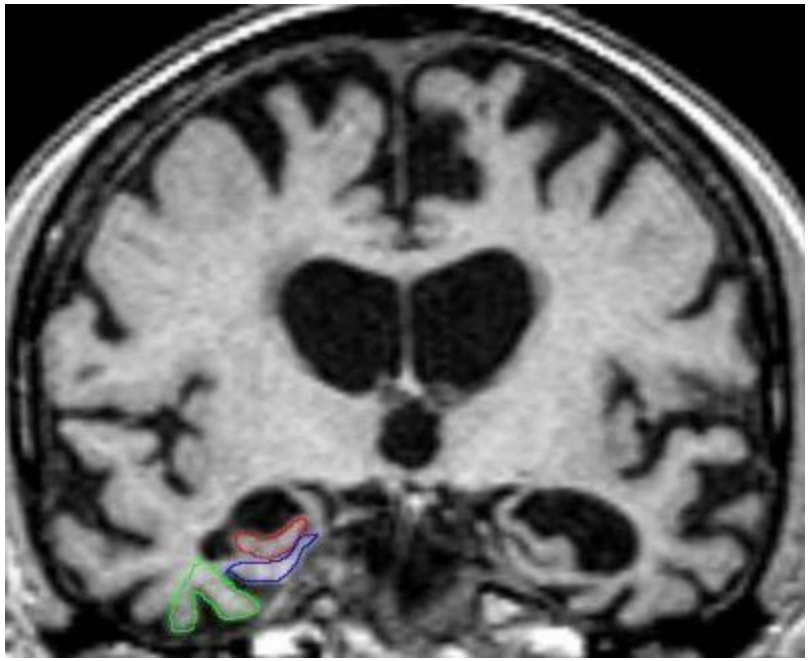
Neuroimaging - Structural imaging: CT & MRI

	For	Against
For the assessment of a person with cognitive impairment, **at least one structural imaging** procedure (CT or MRI of the brain) is recommended to establish the presence of clinically unsuspected cerebrovascular disease and to rule out potentially reversible structural etiologies. (Grade 1B)	**26%**	**74%**
We suggest that a head **MRI is preferred** 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)	**90%**	**10%**

NPH Gross ventricular dilatation, little atrophy



Alzheimer's disease atrophy, especially hippocampi



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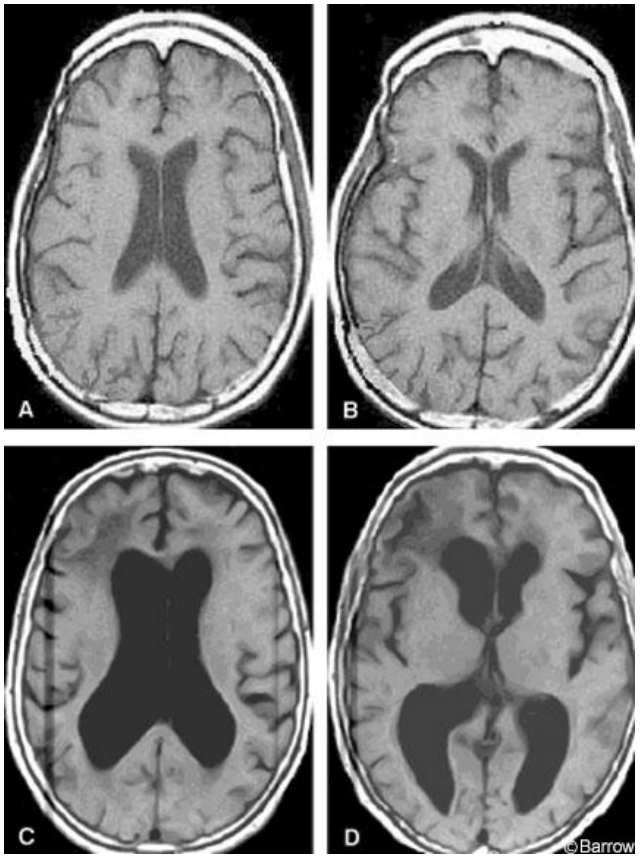

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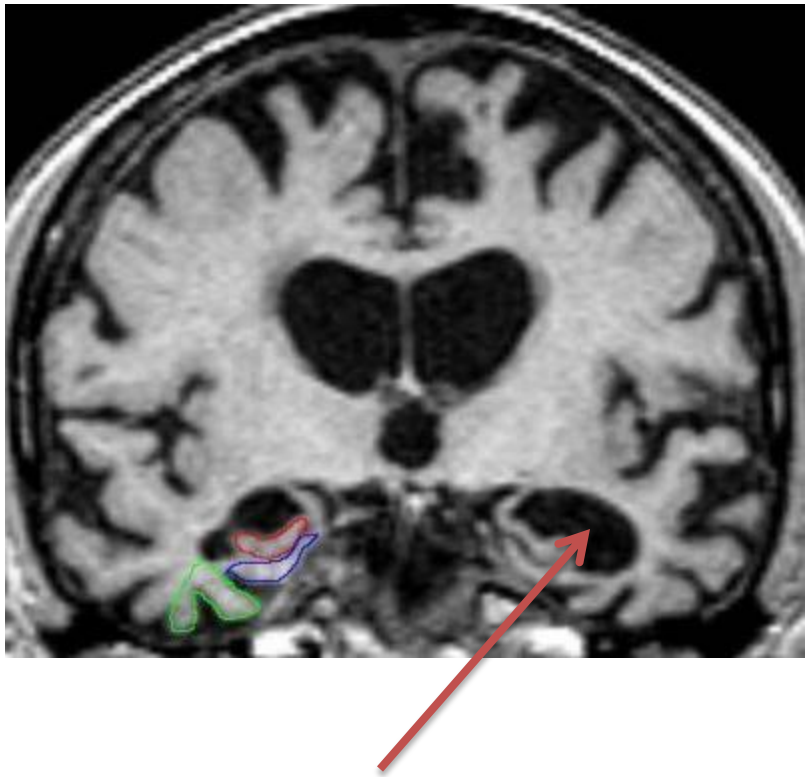


Neuroimaging - Structural imaging: CT & MRI

	For	Against
Standardization of clinical acquisition of core MRI dementia sequences is recommended in Canadian centres 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 1B).	**All**	
We suggest that when available in the clinic, cognition specialists may use the computer **images of the brain to educate a person** with cognitive impairment and family members about changes in the brain. This knowledge may reinforce adherence to vascular risk factor management and to lifestyle modification to improve brain health. (Grade 2C).	**73.3%**	**26.7%**

Neuroimaging – New indication for structural imaging: CT & MRI

For

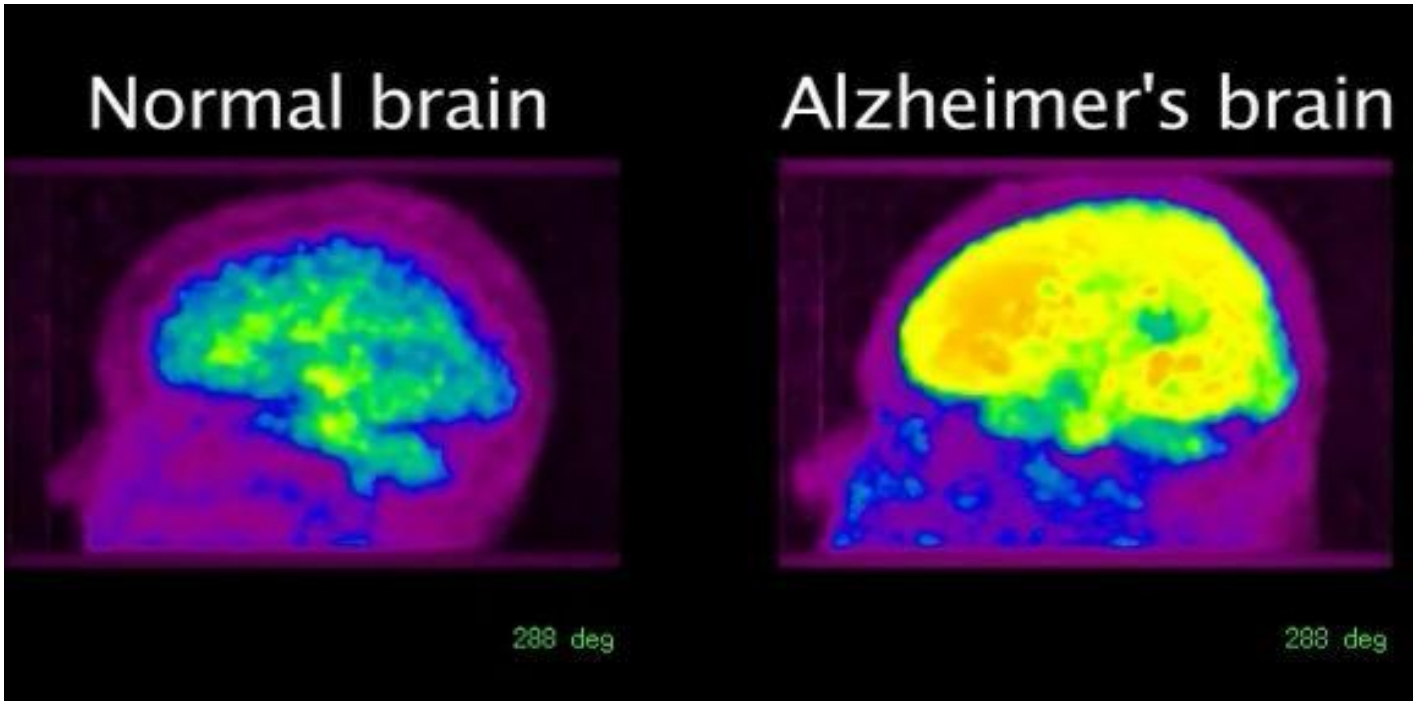
All

In addition to previously listed indications for structural imaging , a CT or MRI should done in the assessment of a person with cognitive impairment **if the presence of unsuspected cerebrovascular disease** would change the clinical management.

Amyloid Imaging

with PiB (Pittsburg compound B)

Florbetapir now approved by FDA



Definitions

Given that the presence of brain amyloid in normal people is of uncertain significance, the CCCD **discourages** the use of amyloid imaging in individuals without memory loss, **outside** of the research setting .

For

All

The medical community should be clear in its discussions with patients, the media and the general population that presence of brain amyloid in **normal** people is of **unclear** significance at the present time.

Neuroimaging - Amyloid Imaging

For

All

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).

Neuroimaging - Amyloid Imaging

	For
Should this technique become available to Canadian clinicians in the future, we recommend **against its use in cognitively normal** individuals or initial investigation of cognitive complaints (Grade 1B).	**All**
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.	**All**

Neuroimaging - Amyloid Imaging

For

All

Amyloid imaging is not currently approved in Canada. Should amyloid imaging become available in Canadian clinicians in the future, it must **not be considered a routine** test and we recommend it 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).

Neuroimaging – PET & SPECT

For

All

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).

All

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, and who cannot be practically referred for an 18F-FDG PET scan*, we recommend that a **SPECT rCBF** study be performed for differential diagnosis purposes (Grade 2C).

Liquid Biomarkers

	For	Against
Plasma Ab1-42 Ab1-42 levels are not recommended for clinical practice.	**All**	
Measures of CSF Ab1-42, total tau and phosphorylated tau at ser 181 are recommended for the biomarker workup of patients with **atypical dementia**.	**64.3%**	**35.7%**
Measures of CSF Ab1-42, 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.	**71.4%**	**28.6%**

Early Onset Dementia

	For
All patients with early onset dementia should be referred to a **memory clinic**, preferably one with access to **genetic counselling** and testing when appropriate.	**All**
The cost of genetic counseling and testing should be covered by public funding.	**All**
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.	**All**

Early Onset Dementia

Research recommendations	For	Against
Considering the rarity of early onset dementia, a **national registry** for interested at risk individuals, mutation carriers and symptomatic patients will facilitate therapeutic research.	**88.9%**	**11.1%**
Health Policy recommendation: This registry should be supported by public funding.	**83.3%**	**16.7%**

Rapidly Progressive Dementia

	For	Against
It is suggested that RPD be defined as a dementia which **develops within 12 months after the appearance of first cognitive symptoms**. (Grade 2C)	**94.1%**	**5.9%**
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)	**94.1%**	**5.9%**
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)	**All**	

Rapidly Progressive Dementia

	For	Against
The diagnostic strategy should emphasize the detection of **potentially curable conditions**, such as infections, immune mediated and toxic metabolic causes. Table 6 outlines such an approach (Grade 2B)	**All**	
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 pharmacological management (Grade 2B)	**94.1%**	**5.9%**

Update on Pharmacological Treatment

Update on Pharmacological Treatment

	For
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 what is (are) felt to be the **predominant** contributing cause(s). (Grade 1B)	**All**
We recommend cholinesterase inhibitors as a treatment option for **Alzheimer's disease with cerebrovascular disease**. (Grade 1B)	**All**

Update on Pharmacological Treatment

	For
Cholinesterase inhibitors are recommended as a treatment option for dementia associated with **Parkinson's disease**. (Grade 1A)	**All**
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 probable or possible **vascular dementia**. (Grade 2B)	**All**
All three cholinesterase inhibitors have demonstrated efficacy for **mild to severe AD**. We recommend a trial of a ChEI for most patients with AD. (Grade1A)	**All**

Update on Pharmacological Treatment

	For	Against
Direct comparisons do not suggest **differences between cholinesterase inhibitors** (Grade 2B). Selection of agent will be based on adverse effect profile, ease of use, familiarity, and differences between the agents in their pharmacokinetics and other mechanisms of action.	**94.1%**	**5.9%**
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)	**All**	

DOMINO study: donepezil and memantine in mod/severe AD

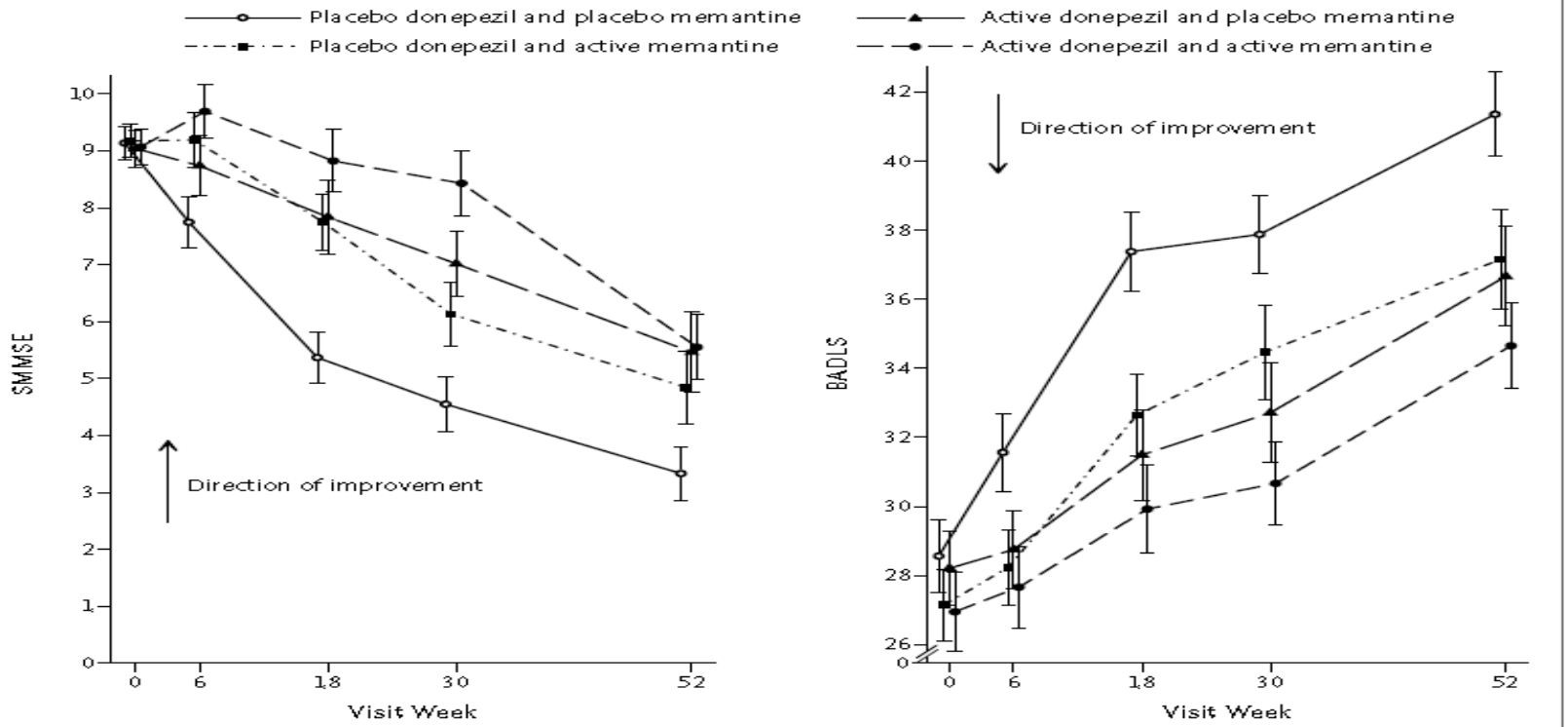


Figure 3. Mean Scores on the Standardized Mini–Mental State Examination (SMMSE) and the Bristol Activities of Daily Living Scale (BADLS), According to Visit Week and Treatment Group.

Scores on the SMMSE range from 0 to 30, with higher scores indicating better cognitive function; scores on the BADLS range from 0 to 60, with higher scores indicating greater impairment. Shown are raw estimates of the mean score at each visit. I bars denote the standard error.

Howard R et al. N. Engl J Med 2012; 366: 892

Update on Pharmacological Treatment

Discontinuing cholinesterase inhibitors in patients with moderate to severe Alzheimer's disease may lead to worse cognitive function and greater functional impairment as compared to continued therapy (Level 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); or,
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.

Continued – Next slide

Update on Pharmacological Treatment

	For	Against
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. (Level 2C)	**83.3**	**6.7%**
If the patient had an inadequate response to non pharmacological interventions or has a major affective disorder, severe dysthymia, or severe emotional lability, we recommend that a trial of an **antidepressant** could be considered. (Grade 2A)	**94.1**	**5.9%**

Update on Pharmacological Treatment

	For
Based on good evidence we recommend that **valproate should *not*** be used for agitation and aggression in AD (Grade 1A)	**All**
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)	**All**

Update on Pharmacological Treatment

	For
We suggest 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)	**All**

Update on Pharmacological Treatment

	For
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)	**All**
There is insufficient evidence to recommend for or against the use of **SSRIs or trazodone** in the management of agitated patients. (Grade 2B)	**All**

Summary

- Emergence of CSF and neuroimaging biomarkers have prompted new recommendations for clinical practice
- Clinical definitions are little changed
- Few new pharmacological recommendations (valproate, memantine)
- EOD and RPD recommendations
- Extensive research agenda

2012 CONFÉRENCE CANADIENNE CONSENSUELLE SUR LA DÉMENCE

2012 CANADIAN CONSENSUS CONFERENCE ON DEMENTIA

CLINICAL PRACTICE GUIDELINES/CONCENSUS STATEMENTS

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

Serge Gauthier, MD, Christopher Patterson, MD, Howard Chertkow, MD, Michael Gordon, MD, Nathan Herrmann, MD, Kenneth Rockwood, MD, Pedro Rosa-Neto, MD, PhD, Jean-Paul Soucy, MD on behalf of the CCCDTD4 participants*

Can Geriatr J 2012; 15(4): 120-6

4th Canadian Consensus Conference on the Diagnosis and Treatment of Dementia

*S. Gauthier, C. Patterson, H. Chertkow, M. Gordon, N. Herrmann, K. Rockwood, P. Rosa-Neto, J.P. Soucy on behalf of the CCCDTD4 participants**.

Can J Neurol Sci. 2012;39: Suppl 5: S1-S8