Diagnosis and Treatment of Alzheimer Disease and Dementia: Results from the Third Canadian Consensus Conference

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HC has been a paid consultant or received honoraria for participation in CME/advisory boards or grant funding from:

Pfizer, Janssen, Lundbeck, Servier, Neurochem, Novartis
Objectives

• To update current diagnosis and treatments for AD and the dementias across the continuum
  – Primary Prevention: rationale
  – MCI: new evidence
  – Mild to Moderate AD: current standards and new approaches
  – Moderate to Severe AD: new rx possibilities
Most asked questions

- Dementia prevention strategies?
- What should we do for MCI?
- When should we use biomarkers to diagnose AD?
- When should we test genes for AD?
- When should we stop cholinesterase inhibitors?
- When should patients stop driving?
- What do you do for mixed dementia?
- Where are the drugs to slow/stop AD?
Any individual with Mild AD should be told to stop driving

Any individual with mild AD and MMSE of less than 24 should be told to stop driving

Any individual with impairment in multiple IADLs or a single ADL should be told to stop driving

Because of anxiety, on-road driving tests are not a fair evaluation of driving ability in a demented individual - neuropsych and clinical testing is better
Regarding mild cognitive states: MCI and CIND are identical labels (European vs. American

Amnestic MCI always leads to Alzheimer Disease

In the >65 year population, there are twice as many individuals with CIND as there are with dementia

The evidence suggests that Donepezil is effective in MCI and should be offered to all MCI patients
Projected Prevalence of Dementia (per 1,000) 1991 - 2031

CSHA Working Group CMAJ 1994; 150: 899-913
Projected Prevalence of AD

300,000 Alzheimer’s Cases Today - > 750,000 Projected Within a Generation

Canadian Study of Health & Aging Working Group. CMAJ 1994; 150:899-913
Other Mixed = 10%

Feldman et al, 2003: Accord Study
Neuroepidemiology, 22; 265-74
Defining Dementia

- A decline from a previous level of function
- Demonstrable impairment of memory (DSM-3)
- Other impairment in at least one of:
  - language (naming)
  - Judgement/frontal lobe function
  - construction/visuospatial function
  - abstraction
  - personality
- Impairment is sufficient to interfere with function and Activities of Daily Living.
- Insidious, and > 6 months (ICD-10)
Facts about dementia and AD

- 250,000 dementia cases in Canada
- 778,000 dementia cases by 2031
- Annual cost = 3.9 billion dollars
- 747/1125 (66%) of dementia cases in CSHA were due to AD
- 95% sporadic
- Incidence / Prevalence ↑ with age

Patterson et al., Can J Neurol. Sci 2001
Ostbye et al., CMAJ 1994
Differential Diagnosis of Dementia

- **AD** 65%
- Other dementias
  - Frontal lobe dementia
  - Creutzfeldt-Jakob disease
  - Corticobasal degeneration
  - Progressive supranuclear palsy
  - Many others
- Lewy body dementias
  - Parkinson’s disease
  - Diffuse Lewy body disease
  - Lewy body variant of AD
- Vascular dementias
  - Multi-infarct dementia
  - Binswanger’s disease
- Vascular dementias and AD
- AD and Lewy body dementias

**Percentages:**
- 5%
- 10%
- 65%
- 5%
- 7%
- 8%

References:
- Small GW et al. JAMA. 1997;278:1363-1371.
Classifying Dementia

Cortical Dementias (68%)
- Alzheimer’s Disease
  - Definite
  - Probable
  - Possible
- Frontotemporal (Picks)
- Focal Dementias
  - Progressive aphasia
  - Semantic dementia

Reversibles (3%)
- depression
- drugs
- tumor
- subdurals
- metabolic
  - Non-reversible 97%

Subcortical Dementia
- Multi-infarct (10%)
- Mixed AD, MID (15%)
- Lewy Body Dem.
- NPH
- PSP
- Other
  - HIV, Parkinsons
Therapeutic Strategies

Induction
- Genetic/hereditary

Pathogenesis
- Traumatisms
- Vascular risk factors

Latency
- Traumatisms
- Vascular risk factors

Detection
- Symptoms

Primary Prevention
- Vaccine
- Estrogen
- NSAID
- Ginkgo

Secondary Prevention
- ("Mild cognitive Impairment")
- Antioxydants
- Anti-inflammatories
- Neural factors
- Estrogens

Symptomatic Treatment
- Cholinergic replacement therapy

Vascular Prevention
ACE-inhibitors are the recommended medication to treat vascular and mixed dementia

There is no specific medication to treat vascular dementia

The presence of vascular lesions increases occurrence of clinical dementia by a factor of 2

The presence of vascular lesions increases occurrence of clinical dementia by a factor of 20
There is insufficient evidence to offer cholinesterase inhibitors or memantine to mild AD patients

Certain cognitive therapy programs (but not general cognitive stimulation) have been demonstrated to improve symptoms of memory loss and delay progression

Cholinesterase inhibitors have proven efficacy at all stages of dementia, and should be carefully considered as therapy

Vitamin E should be offered to all memory impaired individuals to slow rate of progression.
Third Canadian Consensus Conference on Diagnosis and Treatment of Dementia

March 9-11, 2006

Hotel Delta President Kennedy
Montreal, Quebec
Procedure

- Steering committee of national academic leaders (neurology, geriatric medicine, geriatric psychiatry)
- Sponsorship by CNS, C5R, CGS, CAGP, CFPC.
- Funding by CIHR, FRSQ, ASC, sponsoring organizations, and pharma (1/2)
- 8 topics, led by national authorities, with writing committees (42 authors)
- Literature searches, evidence-based reviews
- Preparation of recommendations and background reviews
- Web posting of 203 rec’s, voting by 42 authors
- Consensus = 80% approval
- Discussion at meeting of “non-consensus” recommendations, revision, re-voting.
- 147 recommendations reached consensus
- These were rated as high, medium, low education priorities by an FP panel.
- Only high and medium recommendations are presented here.
## Criteria for assigning levels of evidence

<table>
<thead>
<tr>
<th>Level</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Evidence obtained from at least 1 properly randomized controlled trial.</td>
</tr>
<tr>
<td>2a</td>
<td>Evidence obtained from well-designed controlled trials without randomization.</td>
</tr>
<tr>
<td>2b</td>
<td>Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than 1 centre or research group.</td>
</tr>
<tr>
<td>2c</td>
<td>Evidence obtained from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments are included in this category.</td>
</tr>
<tr>
<td>3</td>
<td>Opinions of respected authorities, based on clinical experience, descriptive studies or reports of expert committees.</td>
</tr>
<tr>
<td>Grade</td>
<td>Criteria</td>
</tr>
<tr>
<td>-------</td>
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</tr>
<tr>
<td>A</td>
<td>There is good evidence to support this manœuvre.</td>
</tr>
<tr>
<td>B</td>
<td>There is fair evidence to support this manœuvre.</td>
</tr>
<tr>
<td>C</td>
<td>There is insufficient evidence to recommend for or against this manœuvre, but recommendations may be made on other grounds.</td>
</tr>
<tr>
<td>D</td>
<td>There is fair evidence to recommend against this procedure.</td>
</tr>
<tr>
<td>E</td>
<td>There is good evidence to recommend against this procedure.</td>
</tr>
</tbody>
</table>
Assessment and management of risk factors, and primary prevention strategies

Christopher Patterson

MacMaster University
Angela Garcia
Chris McKnight
Dessa Sadovnik
Robin Hsuing
The Alzheimer Brain
## Risk factors for developing AD

<table>
<thead>
<tr>
<th>Definite Risk</th>
<th>Putative-Recent</th>
<th>Putative-Older</th>
<th>Protective</th>
</tr>
</thead>
<tbody>
<tr>
<td>age</td>
<td>women</td>
<td>depression</td>
<td>NSAIDS</td>
</tr>
<tr>
<td>Apo E4</td>
<td>Low education</td>
<td>Head trauma</td>
<td>Estrogen?</td>
</tr>
<tr>
<td>Family history</td>
<td>Vascular factors</td>
<td>alcohol</td>
<td>Smoking?</td>
</tr>
<tr>
<td>MCI</td>
<td>Hyper-tension</td>
<td>Aluminum?</td>
<td>Smoking?</td>
</tr>
<tr>
<td></td>
<td>Smoking?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Pharmacological Approach
Vascular Prevention

• Hypertension:
  – Syst-Eur study (Forette et al., Lancet, 1998)
  – PROGRESS Study (Perindopril Protection Against Recurrent Stroke Study, Lancet, 2001)
  – SCOPE Study (Study on Cognition and Prognosis in the Elderly, Int Conf ADAD, 2002)

• Hyperlipidemia (Rockwood et al., Arch Neurol, 2002)
  – Epidemiological data linking use of statins with ↓ prevalence of dementia

• Atrial Fibrillation
• Diabetes
• Smoking

↓ stroke

• The presence of cerebral lacunar infarcts Increases the rate of dementia by a factor of 20

Snowdon et al, JAMA (1997), vol. 277, 813-817
Delaying the onset of AD by 5 years would be associated with a reduction in AD prevalence of 50%.

A modest delay, such as 1 year, would reduce AD/dementia prevalence by 5%.

1. There is good evidence to treat systolic hypertension (>160mm) in older individuals. (Level 1, Grade A) In addition to reducing the risk of stroke, the incidence of dementia may be reduced. The target BP should be 140mm or less.

2. While ASA and statin medications following myocardial infarction; antithrombotic treatment for non-valvular atrial fibrillation; and correction of carotid artery stenosis >60% have been shown to reduce the risk of stroke, (Level 1) there is insufficient evidence to recommend for or against these measures for the specific purpose of primary prevention of dementia. (Grade C)

3. While there are many reasons for treating type 2 diabetes, hyperlipidemia and hyperhomocysteinemia, there is insufficient evidence to recommend treatment of these conditions for the specific purpose of reducing the risk of dementia. (Level 2, Grade C)

4. There is insufficient evidence to recommend for or against the prescription of NSAIDs for the sole purpose of reducing the risk of dementia. (Level 2, Grade C)

5. There is good evidence to avoid the use of estrogens alone or together with progestins for the sole purpose of reducing the risk of dementia. (Level 1, Grade E)
While there is insufficient evidence to make a firm recommendation, physicians may advocate for strategies:
- to reduce head injury
- for greater education
- to wear appropriate protection during administration of pesticides, fumigants, fertilizers and defoliants

There is insufficient evidence to recommend for or against:
- supplementation with vitamins E or C for the prevention of dementia (Level 2, Grade C.)
  - [High dose vitamin E (>400 units/day) is associated with excess mortality and should not be prescribed (Level 1, Grade E.)]
- higher levels of physical or mental activity for the specific purpose of reducing the incidence of dementia.

While there is insufficient evidence to make a firm recommendation for the primary prevention of dementia, physicians may choose to advise their patients about the potential advantages of increased consumption of fish, reduced consumption of dietary fat and moderate consumption of wine. (Level 2, Grade C)
Topic 2

Concept, utility, and management of MCI and CIND

Howard Chertkow, Howard Bergman, Fadi Massoud, Yves Joannette, Ziad Nasreddine, Sylvie Belleville
Complaints in “Normal Cognitive Aging”

- Even “normal” people may complain of memory changes
- Problems include:
  - Trouble concentrating in the presence of distraction
  - Decreased ability to attend multiple channels
  - Difficulty multi-tasking
  - Difficulty recalling names of acquaintances
  - Spatial memory problems
  - Slowing of reaction time
  - Delayed verbal memory becomes mildly decreased
<table>
<thead>
<tr>
<th>Age Group</th>
<th>CIND (n = 861)</th>
<th>Dementia (n = 1132)</th>
</tr>
</thead>
<tbody>
<tr>
<td>65 to 74 yrs</td>
<td>11.0%</td>
<td>2.4%</td>
</tr>
<tr>
<td>75 to 84 yrs</td>
<td>24.0%</td>
<td>11.2%</td>
</tr>
<tr>
<td>&gt; 85 yrs</td>
<td>30.3%</td>
<td>34.7%</td>
</tr>
<tr>
<td>Overall</td>
<td>16.8%</td>
<td>8.0%</td>
</tr>
</tbody>
</table>

Mild Cognitive Impairment

- Memory complaints
- Memory impaired for age (generally 1.5 SD)
- General cognitive function: normal for age
- Normal activities of daily living
- Not meeting dementia criteria
- Clinical Dementia Rating Score of 0.5

Petersen RC et al Arch Neurol 56(3):303-308 1999
1. Physicians should be aware that most dementias may be proceeded by a recognizable phase of mild cognitive decline. Physicians should be familiar with the concept of mild cognitive impairment (or cognitive impairment not dementia) as high risk state for decline and dementia.

2. There is currently inadequate evidence to recommend one term or label (MCI, CIND) over another.

3. There is inadequate evidence to advise MCI patients and their families that the patient is already showing signs of dementia, or to treat MCI as equivalent to dementia. (Recommendation grade C, Evidence level II)

4. There is fair evidence that physicians should closely monitor individuals who have MCI or CIND, because of the known increased risk of both dementia and death that has been documented. (Recommendation grade B, Evidence level II)
Detecting MCI: The MoCA

- Montreal Cognitive Assessment (MoCA), a cognitive screening tool for detection of MCI
  - 30-point scale
  - MCI = MOCA <26
  - Using a cut-off score <26 provides sensitivity of 80%, and specificity of 91% to distinguish MCI from normal
  - Available free in English and French at www.mocatest.org

Nasreddine et al., JAGS, 2005, vol 53, 695-99
5. In cases where there is suspicion of cognitive impairment or concern about the patient’s cognitive status, and the MMSE score is in the “normal” range (24-30), tests such as the MoCA, DemTect, or CMC, could be administered. These would help to demonstrate objective cognitive loss. (Level II, Grade B)

6. There is good evidence that the addition of in-depth neuropsychological testing can be recommended to aid in confirmation of the diagnosis. (Level 1, Grade A)
7. The evidence at the present time is insufficient to conclude that organized cognitive intervention is beneficial to preventing progression in MCI or warrants prescription. (Recommendation Grade C, Evidence level I).

8. There is fair evidence that physicians and therapists should promote engagement in cognitive activity as part of an overall "healthy lifestyle" formulation for elderly individuals with and without memory loss. (Recommendation Grade B, Evidence level I).

9. There is fair evidence that physicians and therapists should promote physical activity at an intensity level that is adapted to the persons' overall physical capacities, as part of a "healthy lifestyle" for older individuals with and without memory loss. (Recommendation Grade B, evidence level II).

10. Current evidence is insufficient to conclude that a specific program of physical training warrants prescription in MCI patients in order to prevent progression to dementia. (Recommendation Grade C, evidence level III).
Common Risk Factors for Developing MCI

- Elevated systolic BP\textsuperscript{1}
- Hypertension\textsuperscript{2}
- Elevated cholesterol in mid-life\textsuperscript{3}
- Low level of education\textsuperscript{4}
- African-American descent\textsuperscript{4}
- Cerebral infarcts evident on MRI\textsuperscript{4}
- Depression\textsuperscript{4}
- Mechanisms may be vascular atherosclerotic mechanisms, or directly through hastening the pathophysiology of AD.

\textsuperscript{1} Launer LJ et al. *JAMA*, 1995; \textsuperscript{2} Carmelli D et al. *Neurology*, 1998; 
Acetylcholine system

Neocortex

Thalamus

Medial septal nuclei

Basal nucleus of Meynert

Hippocampus

Pontomesencephalotegmental complex
Are cholinergic deficits important in AD symptoms?

- Originally decreased cholinergics in AD thought to parallel decreased dopamine in Parkinson Disease
- “Cholinergic Hypothesis of AD” in 1970’s
- Researchers now reject this theory as insufficient
- Decreased Acetylcholine may be non-specific
- Abnormalities in other chemical systems present as well
- GABA, glutamine, Serotonin

Donepezil in MCI

**Objectives**
- To evaluate efficacy & safety of donepezil therapy for treating patients with MCI
- 24-wk, RCT, DB, placebo study in US
- 270 patients with predefined evidence of MCI
- Randomization 1:1 (donepezil:placebo)
  - donepezil (5 mg/d for 6w then 10 mg/d)

**Design**
- Clinical Global Impression of Change for MCI (CGIC-MCI)
- NYU Paragraph Delayed Recall
- NYU Paragraph Immediate Recall; Modified ADAS-cog, WMS-R Digit Span Backwards, Symbol Digit and Patient Global Assessment

Salloway S et al 2003 Neurology S
Patient Global Assessments

Patients (%)

- Donepezil* (n=83)
- Placebo (n=100)

**Improved**
- 61.4% Donepezil
- 51.0% Placebo

**Worse**
- 1.2% Donepezil
- 14.0% Placebo

*P* = 0.007

Fully evaluable at week 24
MCI 3-year Trial with Vitamin E and Donepezil

Memory Impairment = MCI

- Vitamin E
- Donepezil
- Placebo

0 6 12 18 24 30 36

Months

Conversion to AD by Treatment Group

Probability of not converting to AD

- **Donepezil**
- **Vitamin E**
- **Placebo**

- **D–P P=0.416**
- **E–P P=0.912**

Time on MCI study (days)

0 200 400 600 800 1,000 1,200

0.4 0.5 0.6 0.7 0.8 0.9 1.0
Conversion to AD by ApoE Status

Probability of not converting to AD

- ApoE4 negative
- ApoE4 positive

P<0.0001

Time on MCI study (days)
Probability of Converting to AD For Apoe E4 Positive Participants

- Donepezil
- Vitamin E
- Placebo

Time on MCI Study in Days
11. There is currently insufficient evidence to recommend for the use of cholinesterase inhibitors in MCI. (Recommendation Grade C, Evidence level I)
Disease-modifying Treatments

- **Ginkgo Biloba**
  - Mild efficacy
  - Non-regulated product

- **Estrogens**
  - Compelling epidemiological data
  - Disappointing intervention trials

- **NSAID’s/Prednisone**
  - Very mild efficacy
  - Prohibitive side effect profile

- **Vitamine E**
  - One major RCT showed delayed progression of AD (death, institutionalization, deteriorating function and dementia) with high doses (1000 UI BID) (Sano et al., NEJM 1997)
## Clinical Studies in MCI

<table>
<thead>
<tr>
<th>Treatments</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estrogen, combined Estrogen/Progesterone ERT</td>
<td>Negative</td>
</tr>
<tr>
<td>Anti-inflammatories, NSAIDs</td>
<td>Negative</td>
</tr>
<tr>
<td>Statins</td>
<td>Preliminary positive</td>
</tr>
<tr>
<td>Nootropics (Piracetam – pyrrolidine acetamide)</td>
<td>Negative</td>
</tr>
<tr>
<td>AMPA modulator (Ampakine CX516)</td>
<td>Negative</td>
</tr>
<tr>
<td>Anti-oxidants (e.g., Vitamin E)</td>
<td>Mixed results</td>
</tr>
</tbody>
</table>

N.B. None of these treatments are proven or approved

12. There is currently fair evidence to recommend against the use of NSAIDs in MCI. (Recommendation Grade D, Evidence level I)

13. There is currently fair evidence to recommend against the use of estrogen replacement therapy in MCI. (Recommendation Grade D, Evidence level I).

14. There is currently fair evidence to recommend against the use of Ginkgo biloba in MCI. (Recommendation Grade D, Evidence level I).

15. There is currently fair evidence to recommend against the use of vitamin E in MCI. (Recommendation Grade D, Evidence level I)

16. As vascular risk factors and comorbidities impact on the development and expression of dementia, they should be screened for and treated optimally in MCI. (Recommendation Grade B, Evidence level II)
Topic 3

Diagnosis and differential diagnosis of dementia for the primary care practitioner and consultant: clinical laboratory, imaging, markers

Howard Feldman, Hyman Schipper, Alain Robillard, Andrew Kertesz, Claudia Jacova, Dessa Sadovnick
Tiffany Chow, Michael Borrie
Recommendations - clinical diagnosis

- The diagnosis of dementia remains clinical. There is good evidence to retain the diagnostic criteria currently in use. (Grade A, Level II)
- The sensitivity of clinical diagnosis for possible or probable Alzheimer's disease based on the NINDS-ADRSA criteria remains high. The specificity is lower. The continued use of the NINDS-ADRSA criteria is recommended. (Grade A, Level I)
- 'Mild' Alzheimer's disease can be diagnosed with a high degree of specificity, when the presenting clinical picture is one of memory impairment. (Grade B, Level I)
• Neuropsychological testing is a useful adjunct in the diagnosis and differential diagnosis of dementia. (level II grade B)

• The diagnosis and differential diagnosis of dementia is currently a clinically integrative one. Neuropsychological testing alone cannot be used for this purpose and should be used selectively in clinical settings (level II grade B)
Biomarkers
CSF T-Tau:

- 2 Assays:
  - Innogenetics
  - Athena

**Elevated in:**
- Head trauma
- Stroke
- Encephalitis
- Guillain-Barre
- ALS

**But Normal in:**
- Depression
- Parkinson’s Disease
- Alcohol overuse

Felt to be non-specific marker of neuronal destruction

1. Blennow & Hampel (2003), Lancet Neurology
2. Hampel et al., (2004), Archives of General Psychiatry
1. Blennow & Hampel (2003), Lancet Neurology
2. Hampel et al., (2004), Archives of General Psychiatry
Abeta42 ELISA

1. Blennow & Hampel (2003), Lancet Neurology
2. Hampel et al., (2004), Archives of General Psychiatry
CSF ABeta 42

- CSF levels of Total Abeta disappointing as CSF marker
- ABeta 42 is principal component of plaques
- Decreased ABeta 42 found in diverse CNS diseases including:
  - MSA
  - ALS
  - CJD

1. Blennow & Hampel (2003), Lancet Neurology
2. Hampel et al., (2004), Archives of General Psychiatry
CSF ABeta42 Sensitivity

1. Blennow & Hampel (2003), Lancet Neurology
2. Hampel et al., (2004), Archives of General Psychiatry
• Multicentre retrospective review of clinically diagnosed patients with:
  – AD – 150 subjects
  – Controls (healthy & neurologic) – 100
  – Non-AD Dementia:
    • Vascular 33
    • FTD 11
    • NPH 20
    • Other degenerative 15/79
### Specificity of T-Tau, AB42

Hulstaert et al. Neurology 1999;52:1555-1562

<table>
<thead>
<tr>
<th></th>
<th>AD vs. Cntrl</th>
<th>AD vs. other dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AB42</strong></td>
<td>81%</td>
<td>59%</td>
</tr>
<tr>
<td><strong>Tau</strong></td>
<td>70%</td>
<td>57%</td>
</tr>
<tr>
<td><strong>AB42,Tau</strong></td>
<td>87%</td>
<td>58%</td>
</tr>
</tbody>
</table>
Phospho-Tau Antibodies

**Antibody**
- AntiPS199
- HT7

**Epitope**
- P-serine 199
- Tau 159–163

**Specificity**
- Phosphorylated tau
- All forms of tau

**Antibody**
- AT270
- HT7

**Epitope**
- P-threonine 181
- Tau 159–163

**Specificity**
- Phosphorylated tau
- All forms of tau

**Antibody**
- CP9
- CP27
- Tau1

**Epitope**
- P-threonine 231
- Tau 130–150
- Tau 196–205

**Specificity**
- Phosphorylated tau
- All forms of tau
Several Varieties found to be ↑’d in AD

? Reflects abnormal phosphorylation in AD and not neuronal damage more generally?
- P-Tau 18/231, 181, 199, 231, 396/404

Not ↑’d in
- stroke or Creutzfeldt-Jakob dz
- ALS, Parkinson’s
- Depression
- Vascular, frontotemporal, or Lewy Body Dementia
CSF Phospho-Tau Sensitivity
Summary until Now

• AB42 and Total-Tau
  – Highly sensitive tests (80-90%)
  – Highly specific relative to healthy controls
  – But other dementias correctly classified
    • 60% of the time (relative to clinical diagnosis)
    • 70% of the time (relative to pathological diagnosis)

• Phospho-Tau
• Classifies FTD well (spec. 92%)
• VD/LBD classified ~70% correctly
Recommendations on Biomarkers

To Primary Care Physicians

1. Biological markers for the diagnosis of AD should not, at this juncture, be included in the battery of tests routinely used by primary care physicians to evaluate subjects with memory loss (Recommendation Level C). Consideration for such specialized testing in an individual case should prompt referral of the patient to a neurologist or geriatrician engaged in dementia evaluations or a Memory Clinic.
To Specialists

2. Although highly desirable, there currently exist no blood- or urine-based AD diagnostics that can be unequivocally endorsed for the routine evaluation of memory loss in the elderly. The non-invasiveness of such tests, if and when they become available, would be suitable for mass screening of subjects with memory loss presenting to specialists in their private offices and Memory Clinics.

3. Due to their relative invasiveness and availability of other fairly accurate diagnostic modalities (clinical, neuropsychological and neuroimaging), CSF biomarkers need not be performed in all subjects undergoing evaluation for memory loss (Recommendation Level C).
4. a) CSF biomarkers may be considered in the differential diagnosis of AD where there are atypical features and diagnostic uncertainty (level II Level B). For example, CSF biomarkers may prove useful in differentiating frontal variants of AD from FTD.

5. When a decision to obtain CSF biomarkers is made, combined Aβ1-42 and p-tau concentrations should be measured by validated ELISA (Recommendation Level A). It may be best to convey the CSF samples to a centralized facility (commercial or academic) with a track record in generating high-quality, reproducible data.

6. CSF biomarker data in isolation are insufficient to diagnose or exclude AD (Recommendation Level C). They should be interpreted in light of clinical, neuropsychological, other laboratory and neuroimaging data available for the individual under investigation.
Structural Neuroimaging
Atrophy in Alzheimer’s disease

Atrophy of the brain in AD: Medial temporal lobes are affected first and most severely

Figure from: 8. http://pathology.ouhsc.edu/DeptLabs/diagnostic_center_for_alzheimer.htm
Hippocampal volume in Alzheimer’s disease

Dark lines cross the thinnest width of the hippocampus and arrowheads indicate hippocampal boundaries.

©Gao FQ and Black SE, Sunnybrook & Women’s College Health Sciences Centre, U of T
Clarfield criteria for CT:

- age < 70
- new onset dementia, < 1 year
- atypical presentation
- rapid unexplained deterioration
- unexplained focal signs, symptoms
- head injury
- incontinence, gait ataxia
- need for reassurance of patient, family

Recommendations-structural

1. There is fair evidence to support the selective use of CT or MRI scanning in the work-up for dementia – per 1999 Guidelines (Level ii, Grade B)

2. There is fair evidence to support use of structural neuroimaging to rule in concomitant cerebrovascular disease that can affect patient management. (Grade B, Level II-ii)

3. There is fair evidence to support the use of structural neuroimaging to track the progression of AD in clinical trials, especially if the morphometry is combined with neuropsychological testing.
SPECT scan of normal control vs AD

Normal Control  Alzheimer’s Disease

Sandra E. Black-S&W-U of T
1. There is fair evidence that functional imaging with PET or SPECT scanning might assist specialists in the differential diagnosis of dementia, particularly those with questionable early stage dementia or those with frontotemporal dementia. There is variability across centers, with requisite expertise in these modalities that needs to be taken into account in determining utility. (Level II, B)

2. fMRI and MRS scanning are not recommended for use by family physicians or specialists to make or differentiate a diagnosis of dementia in people presenting with cognitive impairment. They remain very promising research tools. (Level of Evidence 3, Grade of Evidence B)
Recommendations – B12, homocysteine

1. It is recommended that serum Cbl (B12) levels be determined in all older adults suspected of dementia or cognitive decline. (Grade B, Level 2)

2. Older adults found to have low Cbl levels should be treated with Cbl (either oral or parenteral forms), because of potential improvement of cognitive function and the deleterious effects of low Cbl levels on multiple organ systems, besides the effects on cognition. (Grade B, Level 2)

3. There is currently insufficient evidence to support the need for serum homocysteine (tHcy) levels to be determined in older adults suspected of dementia or cognitive decline (Grade C, Level 3)

4. There is currently insufficient evidence that treatment of elevated serum homocysteine (tHcy) levels affects cognition. (Grade C, Level 3)

5. Determination of serum folic acid or RBC folate in older adults in Canada is optional, and may be reserved for patients with celiac disease, inadequate diets, or other conditions that prevent them from ingesting grain products. (Grade E, Level 2)
Genetics and Dementia: Risk Factors, Diagnosis, & Management

Ging-Yuek Robin Hsiung  
A. Dessa Sadovnick
Genetic susceptibility risk factors

1. Genetic screening with APOE genotype in asymptomatic individuals in the general population is not recommended because of the low specificity and sensitivity. (Grade E, Level 2)

2. Genetic testing with APOE genotype is not recommended for the purpose of diagnosing AD because the positive and negative predictive values are low. (Grade E, Level 2)
Management of mild to moderate Alzheimer's disease

David Hogan, Malcolm Hing
Peter Bailey, Krista Lanctot
Linda Thorpe
Outcome measures used in AD and AD + CVD trials

- **Cognition** (ADAS-Cog, MMSE)
- **Function** (DAD, ADCS-ADL, BrADL)
- **Global** (CIBIC-plus)
- **Behaviour** (NPI)

Caregiver burden
SCGB, ACTS
# Available AChE inhibitors for AD

<table>
<thead>
<tr>
<th>AChE inhibitor</th>
<th>Selectivity</th>
<th>$T_{1/2}$</th>
<th>Starting dose</th>
<th>Minimal effective dose</th>
<th>Usual recommended dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donepezil</td>
<td>AChEI</td>
<td>Approx. 70 h</td>
<td>5 Qam</td>
<td>5 Qam</td>
<td>5-10 mg/d</td>
</tr>
<tr>
<td>Galantamine</td>
<td>AChEI &amp; Nicotinic modulator</td>
<td>7-10 h</td>
<td>4 bid</td>
<td>8 bid</td>
<td>8-12 bid</td>
</tr>
<tr>
<td>Rivastigmine</td>
<td>AChEI &amp; BuChEi</td>
<td>1-2 h</td>
<td>1.5 bid</td>
<td>3 bid</td>
<td>3-6 bid</td>
</tr>
</tbody>
</table>
Frequency of prescription and cost

MILLIONS OF PRESCRIBITIONS

ARICEPT

EXELON

REMINYL

Source: IMS Health

Cost in Canada: $1825.00/year
Galantamine maintains cognitive benefits in AD over 12 months

Mean change (± SE) in ADAS-Cog/11 from baseline

**Double-blind**

- Galantamine 24 mg / galantamine 24 mg
- Placebo / galantamine 24 mg
- Historical placebo group

**Open-label extension**

- Galantamine 24 mg / galantamine 24 mg
- Placebo / galantamine 24 mg
- Historical placebo group

* p < 0.05 vs placebo / galantamine and NS from baseline

Patients responding to treatment with galantamine 24 mg/day (%)

- Improved or unchanged: 17.6%
- \(\leq 4\)-point increaser: 35.6%
- \(\leq 7\)-point increaser: 43.3%
- \(\leq 10\)-point increaser: 53.3%
- \(\leq 20\)-point increaser: 80.0%

Change in ADAS-Cog score over 36 months

n = 119

However,

- Response to these drugs is variable.
- Changes in psychometric performance gives impression of small effects.
- Are these drugs worth it?
Cholinesterase Inhibitors

Should Be Considered In Patients With Mild To Moderate AD (Standard) Although Studies Suggest A Small Average Degree Of Benefit

Vitamin E (1000 I.U. Po Bid)

Should Be Considered In An Attempt To Slow Progression Of AD (Guideline)
### AChEIs: meta-analysis

**Lanctôt et al CMAJ 2003**

<table>
<thead>
<tr>
<th>Study</th>
<th>Cholinesterase inhibitor</th>
<th>ChEi responders</th>
<th>Placebo responders</th>
<th>Total subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rogers, 1998a</td>
<td>Donepezil</td>
<td>107/305</td>
<td>27/150</td>
<td>455</td>
</tr>
<tr>
<td>Rogers, 1998b</td>
<td>Donepezil</td>
<td>76/298</td>
<td>17/152</td>
<td>450</td>
</tr>
<tr>
<td>Burns, 1999</td>
<td>Donepezil</td>
<td>125/544</td>
<td>38/274</td>
<td>818</td>
</tr>
<tr>
<td>Rösler, 1999</td>
<td>Rivastigmine</td>
<td>149/467</td>
<td>44/220</td>
<td>687</td>
</tr>
<tr>
<td>Raskind, 2000</td>
<td>Galantamine</td>
<td>64/357</td>
<td>27/196</td>
<td>553</td>
</tr>
<tr>
<td>Wilcock, 2000</td>
<td>Galantamine</td>
<td>84/414</td>
<td>33/203</td>
<td>617</td>
</tr>
<tr>
<td>Rockwood, 2001</td>
<td>Galantamine</td>
<td>61/240</td>
<td>24/123</td>
<td>363</td>
</tr>
<tr>
<td>Wilkinson, 2001</td>
<td>Galantamine</td>
<td>59/179</td>
<td>23/83</td>
<td>262</td>
</tr>
</tbody>
</table>
AChEIs: Numbers Needed to Treat
Lanctot et al CMAJ 2003

- For global response: improvement
  - NNT = 12 (95% CI 9-16)
- For cognitive response: improvement 4 pts ADAS
  - NNT = 10 (95% CI 8-15)
- For harm: adverse event
  - NNT = 12 (95% CI –10-18)
- Comparison to other disorders
  - Depression NNT = 4
  - Psychosis NNT = 3
  - 5 year prevention stroke, MI or death = 29-86

All three drugs had similar cognitive efficacy, with donepezil and rivastigmine showing a dose effect across the dosing levels studied.

Dropout rates were greater with galantamine and rivastigmine.
Memantine Voltage Dependency in Alzheimer’s Disease

Resting State
-70 mV

Depolarization
-50 mV

Synaptic Activity
-20 mV

Physiological Magnesium Block

Magnesium

Memantine

Low to Moderate Affinity Antagonist Memantine (Ki = 0.5 µM)

Reprinted from *Neuropharmacology*, Vol 38, CG Parsons, W Danysz, G Quack. Memantine is a clinically well tolerated N-methyl-D-aspartate (NMDA) receptor antagonist—a review of preclinical data, pages 735-767, copyright 1999, with permission from Elsevier.
Memantine Selectively Blocks Pathological Activation of NMDA Receptors

Memantine Blocks Glutamatergic Activation and Chronic Neurodegeneration

Memantine Facilitates Cognitive Activity

Abnormal Pathological Activation of NMDA Receptors

Rest

Memantine Selectively Blocks Pathological Activation of NMDA Receptors

Reprinted from *Neuropharmacology*, Vol 38, CG Parsons, W Danysz, G Quack. Memantine is a clinically well tolerated N-methyl-D-aspartate (NMDA) receptor antagonist—a review of preclinical data, pages 735-767, copyright 1999, with permission from Elsevier.
14a. All three cholinesterase inhibitors available in Canada are efficacious for mild to moderate AD. They are all viable treatment option for most patients with mild to moderate AD. (Grade A, Level I)

14b. While all three cholinesterase inhibitors available in Canada have efficacy for mild to moderate AD, equivalency has not been established in direct comparisons. Selection of which agent to be used will be based on adverse effect profile, ease of use, familiarity and beliefs about the importance of the differences between the agents in their pharmacokinetics and other mechanisms of action. (Grade B, Level I)

14c. All physicians prescribing these agents should be aware of the contraindications and precautions with the use of cholinesterase inhibitors. (Grade B, Level III)
14d. If adverse effects occur with a cholinesterase inhibitor, the agent should either be discontinued (if the side effects are judged to be disabling and/or dangerous), or the dose of the agent should be decreased with an option to retry the higher dose after four weeks if the lower dose is tolerated (if the side effects are judged to be minor in severity). (Grade B, Level III)

14g. Patients can be safely switched from one cholinesterase inhibitor to another. The decision of when to make a switch is based on the judgment of the prescribing physician and the patient (or their proxy). (Grade B, Level III)

14h. Patients can be switched from a cholinesterase inhibitor to memantine. The decision of when to make a switch is based on the judgment of the prescribing physician and the patient (or their proxy). There is no published guidance as to how to switch from a cholinesterase inhibitor to memantine, but a report presented at a meeting indicates that it can be done safely. (Grade B, Level III)
15a. Memantine is an option for patients with moderate stages of AD. Its use in mild stages of AD is not recommended. (Grade B, Level I)

15b. Combination therapy of a cholinesterase inhibitor and memantine is rational (as the medications have different mechanisms of action), appears to be safe and may lead to additional benefits for patients with moderate to severe AD. This would be an option for patients with AD of a moderate severity. (Grade B, Level I)

18d. While Ginkgo biloba is a safe agent, its use can not be recommended for the treatment of dementia. Further methodologically sound trials are required. (Grade C, Level I)
7a. There is good evidence to indicate that individualized exercise programs have an impact on functional performance in persons with mild to moderate dementia. (Grade A, Level 1)

7b. There is insufficient research evidence to come to any firm conclusions about the effectiveness of
   i. cognitive training/cognitive rehabilitation
   ii. environmental interventions
   iii. other non-pharmacological therapeutic interventions in improving and/or maintaining cognitive and/or functional performance in persons with mild to moderate dementia. (Grade C, Level 1)
Recommendations

16. Medications for the treatment of AD should be discontinued when:
   a. The patient and/or their proxy decision-maker decides to stop;
   b. The patient refuses to take the medication;
   c. 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;
   d. There is no response to therapy after a reasonable trial;
   e. The patient experiences intolerable side effects;
   f. The comorbidities of the patient make continued use of the agent either unacceptably risky or futile (e.g., terminally ill); or,
   g. The patient's dementia progresses to a stage where there is no significant benefit from continued therapy. (Grade B, Level III)

17. After stopping therapy for AD, patients should be carefully monitored and if there is evidence of a significant decline in their cognitive status, functional abilities or the development/worsening of behavioural challenges consideration should be given to reinstating the therapy. (Grade B, Level III)
# Anti-Inflammatory studies in AD

<table>
<thead>
<tr>
<th>Drug</th>
<th>Length</th>
<th>Outcome</th>
<th>Subjects</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydroxychloroquine</td>
<td>18 mos</td>
<td>neg</td>
<td>n=168</td>
<td>Van Gool et al</td>
</tr>
<tr>
<td>Prednisone</td>
<td>12 mos</td>
<td>neg</td>
<td>n=138</td>
<td>Aisen et al</td>
</tr>
<tr>
<td>Naproxen</td>
<td>12 mos</td>
<td>neg</td>
<td>n=351</td>
<td>Aisen et al</td>
</tr>
<tr>
<td>Rofecoxib</td>
<td>12 mos</td>
<td>neg</td>
<td>n=351</td>
<td>Aisen et al</td>
</tr>
<tr>
<td>Rofecoxib</td>
<td>12 mos</td>
<td>neg</td>
<td>n=692</td>
<td>Reines et al</td>
</tr>
<tr>
<td>Nimesulide</td>
<td>3 mos</td>
<td>neg</td>
<td>n=40</td>
<td>Aisen et al</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>6 mos</td>
<td>neg *</td>
<td>n=41</td>
<td>Scharf et al</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>6 months</td>
<td>pos</td>
<td>n=</td>
<td>Rogers et al</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>12 mos</td>
<td>neg</td>
<td>n=</td>
<td>abstract</td>
</tr>
</tbody>
</table>
Atorvastatin in AD

- Atorvastatin 80 mg vs placebo
- 12 month RCT mild to moderate AD
- Concurrent AchEIs allowed
- Evaluable data on 63 subjects OC n = 46
- ADAS cog, CGIC benefit reported at 12 months
  - Additional benefit on LDL

Sparks L et al 8th International Montreal Springfield Conference 2004
18a. Vitamin E supplementation is not recommended for the treatment of AD. (Grade E, Level I)

18b. The use of the synthetic antioxidant idebenone is not recommended for the treatment of AD. (Grade D, Level I)

18c. The administration of vitamin B1, B6, B12 and/or folic acid supplements to persons suffering from AD who are not deficient in these vitamins is not recommended. (Grade D, Level III)
Recommendations

18e. The use of an anti-inflammatory drug is **not recommended** for the treatment of the cognitive, functional or behavioural manifestations of a dementia. (Grade D, Level I)

18f. The use of a HMG-CoA reductase enzyme inhibitor is **not recommended** for the treatment of the cognitive, functional or behavioural manifestations of a dementia. (Grade D, Level III)

18g. Hormone replacement therapy (estrogens combined with a progestagen) or estrogen replacement therapy (estrogen alone) is **not recommended** for the cognitive impairments of women with AD. (Grade B, Level I)

18h. There is **insufficient evidence to recommend** the use of androgens (e.g., testosterone) to treat AD in men. (Grade C, Level I)
Vaccination with Aβ peptide prevents memory deficits in an animal model of Alzheimer’s disease (Morgan et al., 2001).

Aβ immunization reduces behavioural impairment and plaques in a model of Alzheimer’s disease (Janus et al., 2001).

Tg2576 transgenic mice
PDAPP Transgenic mice 13 months

Transgenic Mouse: APP mutation

Aβ42- injected mice at 6 weeks

Hippocampal Dentate Gyrus

Slide courtesy of Dr. Howard Feldman

Schenk et al., Nature 1999: 400 173-77
Post Vaccination Meningoencephalitis

Slide courtesy of Dr. Howard Feldman

Nicoll JAR et al Nature Medicine, Apr 2003, 9(4): 448-452
GAG-Mimetics

• Glycosaminoglycans (GAGs) contribute to the amyloidogenic cascade by promoting the Aβ fibrillogenic process that leads to plaque formation
• Can low molecular weight GAG-mimetic compounds that bind to soluble Aβ peptides promote their clearance?
• Neurochem inc.-Alzhemed -Phase 3 trials-first was negative - unable to demonstrate a benefit..second is ongoing
25b. No single brief cognitive test (e.g., MMSE) or combination of brief cognitive tests has sufficient sensitivity or specificity to be used as a sole determinant of driving ability. Abnormalities on cognitive tests such as the MMSE, clock drawing and Trails B should result in further in-depth testing of driving ability. (Grade B, Level III)

25c. Driving is contraindicated in persons who, for cognitive reasons, have an inability to independently perform multiple instrumental activities of daily living (e.g., medication management, banking, shopping, telephone use, cooking) or any of the basic activities of daily living (e.g., toileting, dressing). (Grade B, Level III)

25d. The driving ability of persons with earlier stages of dementia should be tested on an individual basis. (Grade B, Level III)
Driving Recommendations

25e. A health professional-based comprehensive off- and on-road driving evaluation is the fairest method of individual testing. (Grade B, Level III)

25f. In places where comprehensive off and on-road driving evaluations are not available, clinicians must rely on their own judgment. (Grade B, Level III)

26g. For persons deemed safe to drive, reassessment of their ability to drive should take place every 6 to 12 months. (Grade B, Level III)

25h. Compensatory strategies are not appropriate for those deemed unsafe to drive. (Grade B, Level III)
28c. Shared care models for the management of patients with mild to moderate AD and dementia should be developed and evaluated. This will require the acceptance of joint responsibility on the part of primary care practitioners and specialty services in delivering care to patients with dementia. (Grade C, Level III)

28d. Dementia care must be adequately funded and reimbursed. Inadequate remuneration should not be a barrier to the delivery of good dementia care. (Grade C, Level III)
Clinical practice guidelines for severe Alzheimer's disease

Nathan Herrmann
Serge Gauthier
Cognition in MSAD
Donepezil Plus Memantine

Treatment Week

Change From Baseline

LS mean difference

P value

N = 404

Memantine/donepezil

Placebo/donepezil

-3.5
-3
-2.5
-2
-1.5
-1
-0.5
0
0.5
1
1.5
2
2.5
3
3.5

0 4 8 12 18 24

Cognition (SIB)
Moderate to Severe AD


Memantine Plus Donepezil Reduced Behavioral Changes

Change in NPI Score (ITT LOCF)

Memantine + Donepezil

Placebo + Donepezil

6. Patients with severe AD can be treated with ChEIs, memantine or the combination. Expected benefits would include modest improvements in cognition, function and behavior and/or slower decline.[I]

7. Treatment with ChEIs and/or memantine should persist until clinical benefit can no longer be demonstrated. Treatment should not be discontinued simply because of institutionalization.[III]

8. The management of BPSD should begin with appropriate assessments, diagnosis, and identification of target symptoms and consideration of safety of the patient, their caregiver and others in their environment.[III]

9. Non-pharmacological treatments should be initiated first. Approaches that may be useful for severe AD include behavioural management for depression, and caregivers/staff education programs for a variety of behaviours. Music and multi-sensory intervention (Snoezelen) are useful during treatment sessions but longer-term benefits have not been demonstrated.[I]
10. Pharmacological interventions should be initiated concurrently with non-pharmacological approaches in the presence of severe depression, psychosis or aggression that puts the patient or others at risk of harm. [III]

11. Pharmacological interventions for BPSD should be initiated at the lowest doses, titrated slowly and monitored for effectiveness and safety. [III]

12. Attempts to taper and withdraw medications for BPSD after a period of three months of behavioural stability should occur in a standardized fashion. [I]

13. Risperidone, and olanzapine can be used for severe agitation, aggression and psychosis. The potential benefit of these and other antipsychotics must be weighed against the potentially increased risk of cerebrovascular events and mortality. [I]

14. Benzodiazepines should be used only for short periods as p.r.n. agents. [I]

15. SSRIs can be used for the treatment of severe depression. [III]

16. If BPSD fail to improve after appropriate non-pharmacological and pharmacological interventions, refer to a specialty service. [III]

17. There is insufficient evidence to recommend for or against the use of trazadone in the management of non psychotic agitated patients.
Vascular dementia (VaD) and AD+CVD: NINDS−AIREN criteria

• Probable VaD
  – Dementia severe enough to interfere with ADLs
  – CVD (focal signs, CT/MRI evidence of relevant lesions)
  – A relationship between the above two disorders

• Possible VaD
  – Dementia and focal signs, but no confirmatory CT/MRI
  – Temporal relationship between dementia and stroke is unclear
  – CVD with cognitive deficit of subtle onset and variable course

• AD+CVD
  – Possible VaD + clinical/imaging evidence for relevant CVD
Hyperintensities (HI) Affecting ACh WM Tracts

Selden NR et al. *Brain* 1998;121:2249-2257

External capsule HI

Deep white HI

Extensive periventricular HI

RH Swartz, S&W, U of T
Recommendations

Use of non-pharmacologic interventions

1. There is currently insufficient evidence to recommend the use of cognitive training for vascular dementia. (Grade C, Level II-1)

Other therapeutic interventions

2. Investigations for vascular risk factors. It is recommended that vascular risk factors are identified in all patients with vascular cognitive impairment. (Grade C, Level III)

3. Treating hypertension. There is some evidence that treating hypertension may prevent further cognitive decline associated with cerebrovascular disease. There is no compelling evidence that one class of agent is superior to another; calcium channel blockers or ACE-inhibitors may be considered. (Grade B, Level I) Treatment for hypertension should be implemented for other reasons, including the prevention of recurrent stroke. (Grade A, Level I)
Recommendations

4. Antiplatelet therapy with aspirin. There is currently no evidence to support the use of aspirin to specifically treat dementia associated with cerebrovascular disease. (Grade C, Level III) Aspirin or other antiplatelet therapies should be used for prevention of recurrent ischemic stroke in appropriate patients (Grade A, Level I) (AHA Guidelines, Stroke 2006)

5. Nimodipine in vascular dementia. There is insufficient evidence for or against the use of Nimodipine for VaD (Grade C, Level I)

6. Use of memantine. There is some evidence of small magnitude of cognitive benefit that is not captured in global measures for patients with VaD. There is insufficient information to recommend memantine for the treatment of vascular dementia. (Grade C, Level I).
7. Use of cholinesterase inhibitors in dementia due to combined Alzheimer’s and Cerebrovascular Disease: There is fair evidence of benefits of small magnitude for galantamine in cognitive, functional, behavioral, and global measures in AD with CVD. Galantamine can be considered a treatment option for mixed Alzheimer’s with Cerebrovascular Disease. (Grade B, Level 1)

8. Use of cholinesterase inhibitors in probable/possible vascular dementia using the NINDS-AIREN diagnostic criteria:

   a) There is insufficient evidence for or against the use of galantamine; (Grade C, Level 1)

   b) There is fair evidence of benefits of small magnitude for donepezil in cognitive and global outcomes, with less robust benefits on functional measures. Donepezil can be considered a treatment option for Vascular Dementia. (Grade B, Level 1)
Topic 4

Genetic and Dementia

Robin Hsiung
Dessa Sadovnik
From Chromosome to base pairs
Autosomal Dominant Pattern

- only one copy of the disease gene is needed to develop phenotype
Autosomal Recessive Pattern

- two copies of the disease gene are needed to develop phenotype
<table>
<thead>
<tr>
<th>Chromosome</th>
<th>Gene</th>
<th>Phenotype</th>
<th>Pathogenesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>21</td>
<td>APP</td>
<td>Early Onset Alzheimer’s Disease</td>
<td>Missense around Aβ domain, increases Aβ4 production by favouring β-secretase cleavage over α-secretase; duplication also causes Dz</td>
</tr>
<tr>
<td>14</td>
<td>PS1</td>
<td>Early Onset Alzheimer’s Disease</td>
<td>Mainly missense &amp; deletions, favours β-secretase activity over α-secretase, Increase Aβ42 production</td>
</tr>
<tr>
<td>1</td>
<td>PS2</td>
<td>Early Onset Alzheimer’s Disease</td>
<td>Missense mutations, Increase Aβ42 production through increase</td>
</tr>
<tr>
<td>19</td>
<td>ApoE</td>
<td>Risk factor for Late Onset Alzheimer’s Disease</td>
<td>A molecular chaperone involved in cholesterol metabolism, the ε4 allele promotes Aβ42 aggregation in amyloid plaques</td>
</tr>
<tr>
<td>11</td>
<td>SORL1</td>
<td>Risk factor for Late Onset Alzheimer’s Disease</td>
<td>SORL1 acts as a trafficking receptor that prevents BACE cleavage of APP; probably many different mutations – not yet identified</td>
</tr>
</tbody>
</table>
Diagrammatic representation of APP domains

- Signal peptide
- Globular (cys) domains
- Acidic domains
- Growth Promoting region
- Heparin binding site 1
- Copper binding domain (CuBD)
- ZnBD-1
- Heparin binding site 2
- ZnBD-2
- Exon 15
- Glycosylated domains
- CHO
- Transmembrane domain
- Cytoplasmic domain
- Growth Promoting region
- Glycosylated domains
- Transmembrane domain
- Cytoplasmic domain
- Secretase sites
- Aβδαγ

- δ β α γ

Secretase sites
Primary structure of Aβ amyloid

Senile plaque

Amyloid

Congophilic

Angiopathy

β secretase  α secretase  γ secretase

NH2 -----TEEISEVKMDAEFRHDSGYEVHHQKLVFFAEDVGSNKGAIIGLMVGGVVIATVIVITLVMLKKK---COOH
Aβ and Pathogenesis of AD

APP mutations increase β-secretase cleavage

γ-secretase activity increased by PS1/PS2 mutations

Aβ42 peptide
Amyloidogenic

Oligomer aggregate

α-secretase
Non-amyloidogenic

Transmembrane
Extracellular

Intracellular

Aβ
## Genes associated with FTD

<table>
<thead>
<tr>
<th>Chromosome Gene</th>
<th>Gene</th>
<th>Phenotype</th>
<th>Pathogenesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>17q21.1</td>
<td>Tau  (MAPT)</td>
<td>FTDP-17</td>
<td>Missense &amp; splice site mutations, early onset FTD with variable degree of Parkinsonism &amp; motor neuron disease</td>
</tr>
<tr>
<td>17q21.31</td>
<td>PGRN</td>
<td>FTLD-U</td>
<td>Nonsense &amp; deletions leads to haploinsufficiency, wide age of onset 39-85, with variable phenotype with frontal behaviour, PPA, Parkinsonism, &amp; CBD</td>
</tr>
<tr>
<td>9p13.3</td>
<td>VCP</td>
<td>FTD with inclusion body myopathy and Paget’s Disease</td>
<td>Missense mutations,rare</td>
</tr>
<tr>
<td>3p11.2</td>
<td>CHMP2B</td>
<td>Unnamed Danish family with FTD</td>
<td>Missence mutations, rare, only reported in one family</td>
</tr>
</tbody>
</table>
Hypothetic situations for counseling

- II-5 is symptomatic, so she should be the first to test in this family
- III-3 & III-4 are eligible for predictive genetic testing (PGT)
- II-7 & III-4 are still at risk because their mothers died before age of onset
- III-7 would like PGT, but II-6 does not
- III-6 is a minor
- III-5 is pregnant
Relative Risk of AD in a patient with positive family history but no clear autosomal dominant inheritance

<table>
<thead>
<tr>
<th>Number of 1st degree relative affected</th>
<th>Age of Onset</th>
<th>Relative Risk</th>
<th>95% C. I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>60-69</td>
<td>5.3</td>
<td>2.8-10</td>
</tr>
<tr>
<td>1</td>
<td>70-79</td>
<td>2.3</td>
<td>1.4-4.6</td>
</tr>
<tr>
<td>1</td>
<td>80 and over</td>
<td>2.6</td>
<td>1.3-5.</td>
</tr>
<tr>
<td>1</td>
<td>overall</td>
<td>3.5</td>
<td>2.6-4.6</td>
</tr>
<tr>
<td>2 or more</td>
<td>overall</td>
<td>7.5</td>
<td>3.3-8.7</td>
</tr>
</tbody>
</table>

From Table 2.1 Chapter 2. Atlas of Alzheimer Disease
1. predictive genetic testing (PGT) can be offered to “at risk” individuals (Grade B, Level 2). These would include first-degree relatives of an affected individual with the mutation (e.g., children and siblings), as well as cousins.
Recommendations – on testing for genetic risk factors

Genetic susceptibility risk factors

1. Genetic screening with APOE genotype in asymptomatic individuals in the general population is not recommended because of the low specificity and sensitivity. (Grade E, Level 2)

2. Genetic testing with APOE genotype is not recommended for the purpose of diagnosing AD because the positive and negative predictive values are low. (Grade E, Level 2)
Topic 8

Ethical issues in dementia

John Fisk, Lynn Beattie
Martha Donnelly, Anna Byszewski
Frank J. Molnar
Disclosure of the diagnosis of dementia

John D. Fisk, B. Lynn Beattie, Martha Donnelly, Anna Byszewski and Frank Molnar.
1. The process of diagnostic disclosure for persons with cognitive impairment or dementia must begin as soon as the possibility of cognitive impairment is suspected. (Level 3, Grade A: 88%)

- During the initial investigations of complaints or suspicions of cognitive loss, the patient’s understanding and attitudes about cognitive loss and dementia, as well as that of their family members/caregivers should be established.
2. Both the diagnosis of dementia and the disclosure of the diagnosis must be considered processes that provide opportunities for education and discussion. (Level 3, Grade A: 100%)
3. The potential for adverse psychological consequences must be assessed and addressed through education of the patient and family/caregivers. (Level 3, Grade B: 100%)
4. Once a diagnosis is established, this must be disclosed to the patient and their family/caregivers in a manner that is consistent with the expressed wishes of the patient. (Level 3, Grade B:88%)
5. Follow-up plans must be made and discussed at the time of diagnostic disclosure. (Level 3, Grade A: 97%)
6. The process of diagnostic disclosure must be evaluated.
The existence of barriers to the implementation of guidelines for clinical practice in the diagnostic disclosure of dementia must be addressed. This includes, but is not limited to education of primary care physicians about the existence of such guidelines as well as in the early differential diagnosis of and treatment of dementia.
Requirements:

• Primary care physicians must also have available to them knowledge of available support services for patients and their care providers.
Ethical Considerations for Decision-Making for Treatment and Research Participation
• A diagnosis of dementia, or other forms of cognitive impairment, does not preclude competence to provide informed consent for treatment or for participation in research.

• Competency must be considered as the ability to make an informed decision about participation in the particular context of the specific treatment or study.
At present there is insufficient evidence to recommend a specific standardized method for determining the competency of persons with dementia for decision-making for treatment or research.
Therefore, for all research, the procedures that are used to evaluate the ability of the potential subject to understand the nature of the research, the consequences of participation (i.e. potential risks and benefits) and alternative choices must be described.
Clinicians and researchers have to consider the obtaining of consent for treatment and research as a process. One that involves both the patient with dementia and their family or caregivers.
• Since research is commonly conducted in a health care setting, the distinctions between the clinician’s role in the management of the individual’s health care and his/her potential role in the conduct of research must be clearly understood by everyone. So too must the procedures that represent standard care and research.
For the clinician and researchers, it is important to recognize that the interests of the person with dementia and those of a substitute decision-maker may differ.

They have an obligation to determine, to the best of their ability, that the decisions made by proxies regarding treatment and research are based on the prior attitudes and values of the patient.
• As Alzheimer’s disease and other forms of cognitive impairment are often progressive neurodegenerative conditions, the potential that competency for decision-making will change over time must be recognized. This may lead to a change from one of obtaining the patient’s ongoing consent to one of obtaining ongoing assent.

• Throughout treatment and research there is a need for ongoing monitoring and re-affirmation of consent/assent.
Conclusions:

• Mild Cognitive Impairment:
  – No suggested symptomatic/preventative therapy

• Mild to Moderate AD:
  – AchEIs standard of care
  – Amyloid modifying therapies in clinic
  – Guide to driving cessation

• Moderate to Severe AD:
  – Efficacy for donepezil + memantine

• Vascular/Mixed Dementia: CI’s-some evidence
Conclusions:

• Current trials for:
  – amyloid antiaggregants/gamma secretase inhibitors
  – cholesterol modulating drugs
  – other modulators of glial response incl vaccines
  – neurotrophin like agents
  – glutamatergic/AMPA modulating drugs
Regarding mild cognitive states: MCI and CIND are identical labels (European vs. American)

Amnestic MCI always leads to Alzheimer Disease

In the >65 year population, there are twice as many individuals with CIND as there are with dementia

The evidence suggests that Donepezil is effective in MCI and should be offered to all MCI patients
There is insufficient evidence to offer cholinesterase inhibitors or memantine to mild AD patients

Certain cognitive therapy programs (but not general cognitive stimulation) have been demonstrated to improve symptoms of memory loss and delay progression

Cholinesterase inhibitors have proven efficacy at all stages of dementia, and should be carefully considered as therapy

Vitamin E should be offered to all memory impaired individuals to slow rate of progression.
ACE-inhibitors are the recommended medication to treat vascular and mixed dementia

There is no specific medication to treat vascular dementia

The presence of vascular lesions increases occurrence of clinical dementia by a factor of 2

The presence of vascular lesions increases occurrence of clinical dementia by a factor of 20
Any individual with Mild AD should be told to stop driving

Any individual with mild AD and MMSE of less than 24 should be told to stop driving

Any individual with impairment in multiple IADLs or a single ADL should be told to stop driving

Because of anxiety, on-road driving tests are not a fair evaluation of driving ability in a demented individual - neuropsych and clinical testing is better
Funding Support

- FRSQ
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- Alzheimer’s Society of Canada
Industrial Support

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- Novartis Inc.
- Janssen-Ortho Inc.
- Neurochem Inc.
- Lundbeck Inc.