Preventing, diagnosing, & treating dementia
An update on current research

Claudia Jacova, PhD, UBC Division of Neurology & Clinic For Alzheimer Disease and Related Disorders
Prevention is an ongoing process!

- **PRIMARY PREVENTION OF AD/DEMENTIA**
- **SECONDARY PREVENTION OF AD/DEMENTIA**
- **TERTIARY PREVENTION OF AD/DEMENTIA**

**DISEASE BURDEN**

- No clinical symptoms
- Diagnosable Cognitive Impairment
- Diagnosable Dementia

**Pathophysiology of AD/dementia**

**Diagnosable Cognitive Impairment**

**Diagnosable Dementia**
Today’s topics

- **Reducing our RISK FOR AD**
  - Candidate strategies for primary & secondary prevention

- **Obtaining an EARLY DIAGNOSIS**
  - New diagnostic frameworks
  - When is early too early?
  - New cognitive testing approaches

- **TREATING** the symptoms, treating the disease
  - Lifestyle interventions
  - New insights into depression in AD
  - The power of music
Reducing Our Risk for AD
Lifetime risk

- The probability that an individual of a given age develops Alzheimer Disease (AD) during his/her remaining lifespan.
Figure 2: Framingham Estimated Lifetime Risks for Alzheimer’s by Age and Sex

<table>
<thead>
<tr>
<th>Age</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>65</td>
<td>9.1%</td>
<td>17.2%</td>
</tr>
<tr>
<td>75</td>
<td>10.2%</td>
<td>18.5%</td>
</tr>
<tr>
<td>85</td>
<td>12.1%</td>
<td>20.3%</td>
</tr>
</tbody>
</table>
Risk for early-onset AD

- > 5% of people with AD are aged 40-65.
- Specific risk factors for early onset are not known except carrier status for familial autosomal dominant mutations.

*Alzheimer’s Association, Facts & Figures 2010; Alzheimer Society of Canada, Rising Tide Report, 2010*
Early life

Risk factors

Genetic factors
Low socio-economic status

Midlife

Vascular conditions
Depression, vulnerability to stress
Diabetes, obesity
Traumatic brain injury

Later life

Protective factors

Antihypertensive drugs
Rich social network
Mental & Physical activities
Cholesterol-lowering medications (statins)
Anti-inflammatory medications
Diet (fish, Mediterranean)

Age

High education

The goal of risk reduction

- To maintain cognitive health into late life
- To delay the onset of AD symptoms by years

Risk reduction does not mean avoiding AD/dementia altogether
Impact of risk reduction on society

- Delaying onset could dramatically reduce the number of people with AD/dementia in future years.
- An intervention given now would reduce prevalence in 30-50 years by:

  - 50% if delay-to-onset is 5 years
  - 10% if delay-to-onset is 1 year
<table>
<thead>
<tr>
<th>INTERVENTION</th>
<th>TRIAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular risk control</td>
<td>Protective</td>
</tr>
<tr>
<td>Antihypertensive</td>
<td>No benefit</td>
</tr>
<tr>
<td>Cholesterol-lowering</td>
<td>Protective [Folate]</td>
</tr>
<tr>
<td>Folate/B6</td>
<td>Mixed/safety</td>
</tr>
<tr>
<td>Medications/</td>
<td>No benefit</td>
</tr>
<tr>
<td>Nutraceuticals</td>
<td>No benefit</td>
</tr>
<tr>
<td>Anti-inflammatory</td>
<td>No benefit</td>
</tr>
<tr>
<td>Hormonal</td>
<td>No benefit</td>
</tr>
<tr>
<td>Ginkgo biloba</td>
<td>No benefit</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>Mixed/safety</td>
</tr>
<tr>
<td>Selenium</td>
<td>No benefit</td>
</tr>
<tr>
<td>Lifestyle</td>
<td>Protective</td>
</tr>
<tr>
<td>Mental activity</td>
<td>Protectivemixed/safety</td>
</tr>
<tr>
<td>Physical activity</td>
<td>Protective</td>
</tr>
<tr>
<td>Stress management</td>
<td>Protective</td>
</tr>
</tbody>
</table>

Forette et al 2002; Durga et al 2007; Small et al 2006; Mahnke et al 2006; Lautenschlager et al 2008;
Heads Up Keeping Your Brain Fit

**BRONZE**
- Concentrate more mindfully on what I’m doing.
- Memorize three frequently-used phone numbers.
- Watch less TV. Ideas: Read a book, do a crossword or sudoku, play a social game (i.e. cards).
- Seek out new experiences.

**DID YOU KNOW...**
- Most Canadians (78%) think brain health is as important as physical health, but aren’t sure what it takes to keep our brains healthy.
- What's good for your heart is good for your head - healthy nutrition and exercise can help reduce your risk for developing Alzheimer's disease or another form of dementia.

**MAKING A PLAN: MIND, BODY, SPIRIT**

The information offered here will guide you, and help you set goals.

- Get started on your brain health plan...

**SILVER**
- Do some mental arithmetic every day.
- Memorize five items on a “to do” list.
- Read newspapers and stories and memorize key points.
- Repeat the story to someone else.
- Memorize a favourite recipe, team roster or sequence of phone numbers.

**GOLD**
- Learn a language or take an evening class.
- Memorize seven items on a “to do” list.
- Memorize a poem.
- Try harder to remember names and faces, birthdays of friends, etc.

http://www.alzheimerbc.org/
## Population attributable risks

- Percentage of AD cases due to a risk factor, taking into account the risk factor’s prevalence

### THE WORLD

- Diabetes
- Midlife hypertension
- Midlife obesity
- Depression
- Physical inactivity: 12.7%
- Smoking: 13.9%
- Low education: 19.1%

### THE US

- Diabetes
- Midlife hypertension
- Midlife obesity
- Depression: 14.7%
- Physical inactivity: 21.0%
- Smoking: 10.8%
- Low education

*Barnes & Yaffe, Lancet Neurology 2011*
Does depression cause AD?

- Earlier-life depression (age < 60) carries a 2- to 4-fold increased risk for AD
- Risk remains the same at different lag times (none, 2-y, >4-y)
- Recurrent depressive episodes carry a higher risk than single episode

The relationship between depression and dementia is complex but depression is more than just an early manifestation of AD

Byers & Yaffe, Nature Neurology 2011
Does antidepressant treatment reduce the risk?

- An important but not well researched question:
  - Risk for AD/dementia similar in subjects with history of depression and subjects with history of taking antidepressants
  - Exposure to antidepressants does not modify risk for AD/dementia

Saczyński et al Neurology 2010; Jorm Gerontology 2000
Obtaining An Early Diagnosis
A. Presence of an episodic memory disorder (core clinical feature)

+ biomarker support:

B. Structural: Atrophy of medial temporal lobe (MRI) and/or

C. Biochemical: Footprint of the neurodegenerative changes of AD (CSF Abeta 1-42, t-tau, p-tau) and/or

D. Molecular neuroimaging: PET FDG; amyloid ligands

Hypothetical model of biomarkers in AD: change from normal to maximally abnormal (y-axis) plotted as a function of disease stage (x-axis)

Hypothetical model of biomarkers in AD: change from normal to maximally abnormal (y-axis) plotted as a function of disease stage (x-axis)

Hypothetical model of biomarkers in AD: change from normal to maximally abnormal (y-axis) plotted as a function of disease stage (x-axis)

*Sperling et al, Alzheimer’s & Dementia 2011; Jack et al, Lancet Neurology 2010*
Amyloid-beta plaques

Courtesy of Dr. Ian Mackenzie
Amyloid-beta plaques in normals

- The brains of >30% of people with normal cognition during life show amyloid plaques at autopsy
- ~35% of people with normal cognition have a positive amyloid-tracer PET scan
- Amyloidosis may be associated with subtle cognitive symptoms but the evidence is mixed

*Bennett et al Neurol 2006; Kantarci et al Neurol 2012*
Would all people with amyloid+ scans develop AD if they lived long enough?

What if some did not?

Could there be yet unknown processes that allow some people to have silent AD?

Wolk & Klunk Curr Neurol Neurosci Reports 2009; Iacono et al Neurol 2009
Cognitive testing in the clinic

Between a rock and a hard place

- Brief cognitive tests provide limited information (sensitivity, domains, underlying disease)
- Neuropsychological testing has limited availability (access, wait times)

Jacova et al. Alzheimer’s & Dementia 2007
Are computerized cognitive tests valid?
In 2012 in the US 53% of 65+

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Internet Use (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 to 24</td>
<td>85</td>
</tr>
<tr>
<td>25 to 34</td>
<td>66</td>
</tr>
<tr>
<td>35 to 44</td>
<td>60</td>
</tr>
<tr>
<td>45 to 54</td>
<td>51</td>
</tr>
<tr>
<td>55 to 64</td>
<td>32</td>
</tr>
<tr>
<td>65 to 74</td>
<td>11</td>
</tr>
<tr>
<td>75 and over</td>
<td>5</td>
</tr>
</tbody>
</table>

1. Includes individuals using the Internet in the 12 months preceding the survey. Excludes 'Don't know' and 'Not stated.'

<table>
<thead>
<tr>
<th>Test</th>
<th>Domains</th>
<th>Discrimination</th>
<th>Usability</th>
<th>Administration &amp; Setting</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS Vital Signs</td>
<td>Memory, psychomotor speed, reaction time, attention, cognitive flexibility</td>
<td>MCI and mild dementia from normal</td>
<td>User interface (UI) minimally considered</td>
<td>Self-administered after setting up battery Office</td>
</tr>
<tr>
<td>Cogstate</td>
<td>Psychomotor speed, attention, working memory, learning</td>
<td>MCI from normal</td>
<td>UI minimally considered Culturally fair</td>
<td>Self-administered after setting up battery Office</td>
</tr>
<tr>
<td>CANS-MCI</td>
<td>Memory, symbol fluency, executive functions</td>
<td></td>
<td></td>
<td>Self-administered after setting up battery Office</td>
</tr>
<tr>
<td>NeuroTrax Mindstreams</td>
<td>Memory, attention, verbal fluency, attention, working memory, information</td>
<td></td>
<td></td>
<td>Administered with assistance of technician Office</td>
</tr>
<tr>
<td>C-TOC (Cognitive Testing On Computer)</td>
<td>Memory, attention, processing speed, visual construction, language, executive function</td>
<td>1) MCI and mild dementia from normal 2) AD from non-AD dementia</td>
<td>UI driving factor in development Culturally fair</td>
<td>Self-administered Office or home</td>
</tr>
</tbody>
</table>

*Jacova et al. Alzheimer’s & Dementia 2010, 2012; Invention Disclosure UBC UILO 2011*
Describe the picture with a complete sentence. Use as many words as you possibly can. When you are finished, click Done.

Are Three Sisters Cat

Tigers Is Looking Two

Door Between Orange Window

Smiling The Through Cats

Build your sentence here:
Usability interview
Clinic patients

C-TOC.v1

Evaluation by cultural advisory panel cycle 1

Test language must be simple

C-TOC.v2

Evaluation by cultural advisory panel cycle 2

Audio support an absolute necessity

C-TOC.v3

Evaluation by cultural advisory panel cycle 3

Computer literacy a huge barrier

C-TOC.v4

People would do the test only if their doctor told them to

Instructions:
Any text is too long

Avoid clutter on the screen

Provide reassurance, e.g.
You are on the right track!

Always enable clicking: people dislike just waiting

Proof-of-concept validation: Detection of MCI

Will computerized cognitive tests work at home?
Lots of reasons in favour of the home

- Older people are likely at their best at home:
  - more vulnerable than younger people to stressors before and at testing
  - more affected by time of day (do best in the morning)
  - prefer their own computers or tablets to devices they have never used

- Access for people with reduced mobility or living in remote locations

Field study

- Interruptions are frequent, pervasive and likely to intrude even when test-taking is carefully scheduled

Tang et al. Grand NCE AGM 2010
physiological
emotional
mental
behavioural

INTERNAL

household

social
technological

EXTERNAL

audible
visual

MESSAGE WAITING
Should cognitive tests be publicly accessible online?

15-minute online test for dementia: DIY memory quiz detects early signs of Alzheimer's in people as young as 50

By FIONA MACRAE
UPATED: 00:23 GMT, 14 May 2011

An early warning test for Alzheimer's that can be taken online in 15 minutes has been developed by British scientists. It can spot signs of the debilitating brain disease in people as young as 50.

The computer-based interactive quiz provides an instant result and could help delay or prevent the condition by advising simple diet and lifestyle changes.

Experts say that delaying the onset of Alzheimer's by five years could halve the number who die with the condition, currently a third of over-60s. This has led scientists around the world to try to create blood and other tests that spot the disease early.
Some minimal standards

- Review process and expert endorsement
- Assurance of privacy and confidentiality
- Accurate information on test results ahead of testing
- Mechanism for monitoring / troubleshooting test performance
- Test results ethically defensible (no online test is a diagnosis)

Courtesy of Julie Robillard
Treating the symptoms; treating the disease
Medical conditions

Dementia

Other Medical Conditions

- Medical conditions that predispose to dementia
- Dementia worsened by medical conditions

Courtesy of Dr. Philip Lee
Are there benefits not measured by current instruments?

How long do benefits really last?

Is there a time medications should be stopped?

The BC Alzheimer’s Drug Therapy Initiative (ADTI) research program will provide much needed answers.
“Given that drug companies aren’t even close to finding Alzheimer’s disease prevention treatment and there are no approved drugs to stop the disease progressing, [Dr.] McGeer said there’s evidence for people trying some safe and simple measures in their own kitchens.”
Depression in AD

- Under-recognized when diagnosed with DSM (standard) criteria
- Provisional New criteria include AD-specific symptoms, for example social isolation or withdrawal
- By provisional New criteria:
  - Prevalence estimates range from 27.4 to 53.6% (median = 44%);
  - Much higher than prevalence estimates by DSM criteria (range 9.3 to 34.8%; median = 14%).

Sepehry et al. American Academy of Neurology Annual Meeting March 2013
Percentage of patients diagnosed with different depression criteria

- Meet DSM & New criteria: 44%
- Meet only New criteria: 53%
- Meet only DSM criteria: 3%

Vilalta-Franch et al. AJGP 2006
What is Music Therapy

“The systematic application of music as planned by an accredited music therapist to bring about positive change.”

Assumed to produce benefits by stimulating many brain areas through:

- Singing
- Vocal improvisation
- Whistling
- Playing percussion instruments
- Reminiscing
- ... and more

Courtesy of Dr. Kevin Kirkland
Does Music Therapy work?

- Cognition? Not so much...

<table>
<thead>
<tr>
<th>Study name</th>
<th>Time point</th>
<th>Statistics for each study</th>
<th>Hedges's g and 95% CI</th>
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</thead>
<tbody>
<tr>
<td>Brotons et al., 2000 END</td>
<td>END</td>
<td>Hedges's Standard g: 0.584, Error: 0.234</td>
<td>Lower limit: 0.126, Upper limit: 1.042, p-Value: 0.012</td>
</tr>
<tr>
<td>Guetin et al., 2009 END</td>
<td>END</td>
<td>Hedges's Standard g: -0.049, Error: 0.381</td>
<td>Lower limit: -0.796, Upper limit: 0.698, p-Value: 0.897</td>
</tr>
<tr>
<td>Groene, 1993 END</td>
<td>END</td>
<td>Hedges's Standard g: 0.119, Error: 0.178</td>
<td>Lower limit: -0.231, Upper limit: 0.468, p-Value: 0.506</td>
</tr>
<tr>
<td>Silber, 1999 END</td>
<td>END</td>
<td>Hedges's Standard g: -0.008, Error: 0.460</td>
<td>Lower limit: -0.910, Upper limit: 0.895, p-Value: 0.987</td>
</tr>
</tbody>
</table>

- Behavior, mood, social interaction? Promising data from small trials...

Sepehry et al., Canadian Conference on Dementia, Montreal 2011
UBC Music Therapy trial

Screening of subjects
Must have BPSD

Assessment of patient behavior, mood, quality of life, cognition,
Assessment of caregiver burden, distress and appraisal
Measurement of salivary cortisol and chromogranin A: physiological stress indicators

Randomization

Music Therapy once weekly for 12 weeks
Group sessions

Usual care & waiting for Music Therapy after 24 weeks

Assessment of patient behavior, mood, quality of life, cognition,
Assessment of caregiver burden, distress and appraisal
Measurement of salivary cortisol and chromogranin A: physiological stress indicators

Usual care after Music Therapy for 12 weeks

Usual care & waiting for Music Therapy after 24 weeks

Assessment of patient behavior, mood, quality of life, cognition,
Assessment of caregiver burden, distress and appraisal
Measurement of salivary cortisol and chromogranin A: physiological stress indicators

Alzheimer Society of Canada grant to Drs. Hsiung, Jacova, Kirkland, Beattie
Takeaways

- **Risk reduction:** Can we do it?
  - Yes! There are tried and proven strategies that each one of us can use.

- **Early diagnosis:** Is it possible before dementia onset? Is it advisable?
  - Yes! Pre-dementia diagnosis is feasible though currently only used in research settings. Personal preferences must be respected.

- **Treatment:** What are realistic strategies and goals?
  - Treatment of AD remains symptomatic. Non-pharmacological ≠ non-effective, with potentially significant alleviation of behavioral and psychological symptoms.
"I follow my doctor's orders religiously. He said for me to spend two hours a day on the tennis court."
Alzheimer Research Unit

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