History of AD and other Dementia’s (Neurocognitive Disorder)

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My Opinion is:

• Whatever you try it will not work over night – In fact to may take years

• Omega (fish oil) may take two years to 2 ½ years

• Brain exercises must be done over time and become more difficult

• Life style changes brushing teeth, dancing, crosswords, games (scramble), diet, etc. consistent and overtime, no quick fixes here

• Apo E 4 is important

• We need to start thing outside of the box
NINTH CENTURY B.C. EGYPT

• Earliest known record of chronic forgetfulness

• Third century possible 1st description of Alzheimer’s

• Fourteenth century England 1st verbal exam to screen for memory issues (coming soon)

• Nineteenth century Emil Kraepelin Dementia Praecox
History of AD and other Dementia’s (Neurocognitive Disorder)

• The history of dementia is probably as old as mankind itself

• About 2,400 years ago Plato described an illness that “gives rise to all manners of forgetfulness as well as stupidity.”

• *Dementia in the Greco-Roman World* also quotes the Roman poet, Juvenal, who almost 2,000 years ago characterized a phenomenon that’s easily recognized as dementia:

> “Diseases of all kind dance around the old man in a troop. But worse than any loss in the body is the failing mind which forgets the names of slaves, and cannot recognize the face of the old friend who dined with him last night, nor those of the children whom he has begotten and brought up.”
History of AD and other Dementia’s (Neurocognitive Disorder)

• During the Dark Ages, advancement in understanding of dementia halted abruptly. There’s no doubt that dementia continued to afflict people in the times between Antiquity and the Enlightenment, but it was hardly written about

• The next notable leap in understanding of dementia after ancient times was in the early 1600s by English philosopher Francis Bacon, who authored a work called *Methods of Preventing the Appearance of Senility*. Bacon may have been the first to recognize dementia as a brain disease
History of AD and other Dementia’s (Neurocognitive Disorder)

Roger Bacon (c. 1220-1292)
- Franciscan friar
- English philosopher
- Oxford professor

- Old age could be thwarted off by:
  - eating a controlled diet
  - proper rest
  - exercise
  - moderation in lifestyle
  - good hygiene
  - inhaling the breath of a young virgin
Emma de Beston

• A record of an Examination of Emma de Beston in Cambridge 1383.exists. Emma was asked
• 1. whence she came, said she didn’t know.
• 2. She knew there were seven days in the week but could not name them.
• 3. She said she had had 3 husbands but couldn’t name one.
• 4. She was asked how many shillings there were in 40 pence. She did not know.
• 5. Asked if she would take 40 silver groats or 40 pence she said they were the same value.
• They found she was not of sound mind having neither sense nor memory nor sufficient intelligence to manage herself her lands and her goods. By inspection she had the face and countenance of an idiot.
History of AD and other Dementia’s (Neurocognitive Disorder)

• It’s also widely recognized by historians, including Berchtold and Cotman, that many of the victims of the 17th century witch trials in Europe and the United States who were burned at the stake may have been simply afflicted with dementia.

• Public understanding of dementia didn’t enter the modern age until the German psychiatrist, Alois Alzheimers, described the first case of what we now know as Alzheimer’s Disease in 1910, classifying it as a subtype of “senile dementia.”
Two Biblical Miracle Herbs Now Shown to Help Alzheimer's

• **Rosemary** is known as the “herb of remembrance” and is the plant that once sheltered the Virgin Mary in her flight to Egypt.

• As a Biblical healing plant, it has long been used to enhance memory as well as lessen heart palpitations, increase energy, cure cataracts, and aid many other health problems.

• Ancient healers used **sage** not only to improve memory and brain function, but also for such diverse conditions as heart blockages, infertility, and extending longevity, among others.
Who has had Dementia and helped along the way?
The global impact of dementia

46.8 million people worldwide are living with dementia in 2015. This number will almost double every 20 years.

Much of the increase will take place in low and middle income countries (LMICs): in 2015, 58% of all people with dementia live in LMICs, rising to 83% in 2050.

BUT!
Declining Dementia Rates

• Senior citizens today are better educated than even half a generation ago

• People with more education tend to earn more money and have better access to health care. They’re less likely to smoke, more likely to exercise and less likely to be overweight. People with more education also may live in safer neighborhoods and have less stress

• People who are better educated may have more intellectually stimulating jobs and hobbies that help exercise their brains
Grim Picture of Alzheimer's in Aging Baby Boomers

• More than 28 million baby boomers will have Alzheimer's disease (AD) by 2050, and they will account for nearly 25% of Medicare spending by 2040, according to a new analysis.

• The risk of Alzheimer's increases with age, and as baby boomers get older — because of the size of the generation — the number of people developing the disease will rise to levels far beyond anything we've seen. The size of this generation is the major factor here.
If it is not AD then what is it?

<table>
<thead>
<tr>
<th>Normal Aging</th>
<th>AD (Alzheimer's disease)</th>
<th>VaD (Vascular dementia)</th>
<th>DLB (Dementia w/Levy bodies)</th>
<th>FTLD (Frontotemporal lobe dementia)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Reduced speed of mental processing and choice reaction times</td>
<td>• Short-term memory loss, impaired executive function, difficulty with activities of daily living, time and spatial disorientation, language impairment, personality changes</td>
<td>• Impaired abstraction, mental flexibility, processing speed, and working memory</td>
<td>• Visual hallucinations</td>
<td>• Progressive behavioral and personality changes that impair social conduct (apathy, disinhibition, etc.)</td>
</tr>
<tr>
<td>• Benign forgetfulness that is mild, inconsistent, and not associated with functional impairment</td>
<td>• Short-term memory loss, impaired executive function, difficulty with activities of daily living, time and spatial disorientation, language impairment, personality changes</td>
<td>• Verbal memory is better preserved</td>
<td>• Cognitive fluctuations</td>
<td>• Language impairment</td>
</tr>
<tr>
<td></td>
<td>• Reduced speed of mental processing and choice reaction times</td>
<td>• Slower cognitive decline</td>
<td>• Visuospatial, attention, and executive function deficits are worse</td>
<td>• Possibly preserved episodic memory</td>
</tr>
</tbody>
</table>
1. □ memory complaints
   □ Objective memory loss (MMSE:  MOCA:  )
   □ Preservation of function
   □ General condition normal
   □ no other explanation for memory loss

2. □ Cognitive decline within 3 months of CVA / TIA
   □ Focal neurological symptoms
   □ Focal neurological signs
   □ Abrupt onset / stepwise decline
   □ Previous CVA or TIA

   □ Vascular Dementia (VAD)
   Mixed AD/VAD

3. □ Visual hallucinations – (detailed / recurrent)
   □ Pronounced fluctuation in cognition over hours / days
   □ Parkinsonism (especially rigidity) /
     bradykinesia
   □ Executive function worse than memory
   □ Neuroleptic sensitivity
   □ Unexplained falls / loss of consciousness

   □ Lewy Body
   Dementia

4. □ Behavioral changes: disinhibition / apathy
   □ Impulsivity / poor judgment
   □ Self neglect / socially inappropriate
   □ Executive function worse than memory
   □ Language problems
   □ Abnormal gait

   □ Frontotemporal
   Dementia

5. □ Incontinence early in course of dementia
   □ Rapidly progressing dementia
   □ gait abnormality

   □ Normal
   Pressure
   Hydrocephalus
AD Research

AD research continues in many different areas

We will review some of the following:

• Treatment - drugs
  - non-pharmacological therapies

• Prevention - epidemiology (the branch of medicine that deals with the incidence, distribution, and possible control of diseases and other factors relating to health)
  - risk factors

• Diagnosis - Genetics
  - biomarkers (imaging, CSF, serum)

• An extended family in Colombia with a genetic mutation causing Alzheimer’s may help scientists prevent the disease someday
Alzheimer’s Disease Theories

• No new drug has been marketed for nearly 20 years
• A number of theories have been proposed to explain the cause of AD but to date, no one theory can adequately explain all aspects of the disease
• Precise mechanisms for AD progression are also unclear
• There are 3 major theories (Cholinergic, Amyloid, Tau) that are currently regarded as the most likely explanation for AD
• They are being used as the basis for therapeutic development
Amyloid Cascade Hypothesis

- This has been the main focus of research to date
- Beta-amyloid (Aβ) is the main component of amyloid plaques (one of the pathological hallmarks of AD)
- Scientists now have a detailed understanding of how this protein fragment is clipped from it’s parent compound amyloid precursor protein (APP) by two enzymes – beta-secretase and gamma-secretase
- Researchers are developing medications aimed at every point in the amyloid processing pathway
Neurofibrillary Tangles (NFT’s)

• It has been postulated that after the deposition of amyloid plaques that a cascade ensues

• This leads to inflammation and ultimately formation of neurofibrillary tangles (NFT’s) – the other major hallmark of AD

• This causes problems with neurotransmitters and neuronal function in the brain and ultimately neurone death
Anti-Amyloid strategies - Immunotherapy

• Initial studies showed that injecting animals with beta-amyloid lead to a good antibody response and clearing of the amyloid plaques from their brains

• Subsequent human studies were prematurely ceased (2002) due to development of brain inflammation (meningoencephalitis) in 6%

• However, there was evidence that the treatment had removed amyloid plaque

• The concept of active immunisation hasn’t been abandoned yet – several pharmaceutical companies are in the early phases of developing new active vaccines
Anti-amyloid strategies - immunotherapy

• As an alternative to actively immunising with beta-amyloid, the next studies looked at “passive immunisation”
• This bypasses the need to respond to an antigen
• Passive immunotherapy remains the leading approach today to disease–modifying treatment for AD
• These monoclonal antibodies target various domains of the beta-amyloid peptide and prevent aggregation or speed up removal
Monoclonal antibodies

• To date, a number of monoclonal antibodies have been studied in clinical trials including bapinezumab and gantenerumab but were stopped prematurely due to lack of perceived efficacy

• However analyses of some subgroups have shown benefits that have lead to further studies

• There are still a number of other monoclonal antibodies that are being actively studied and some are showing early positive results—solanezumab, crenezumab and adecanumab – we await the outcomes of these studies
Bapineuzumab for mild to moderate Alzheimer's disease in two global, randomized, phase 3 trials

• Phase 3 global trials confirmed lack of efficacy of bapineuzumab at tested doses on clinical endpoints in patients with mild to moderate AD. Some differences in the biomarker results were seen compared with the other phase 3 bapineuzumab trials. No unexpected adverse events were observed.

• Pfizer and Johnson & Johnson announced the failure of a second Phase III trial of bapineuzumab, an anti-amyloid antibody...
Solanezuma

• Study results released today show potential disease-modifying effects of the antiamyloid solanezumab (Eli Lilly and Company), with the drug showing some benefits in cognition and function when started early in the course of the disease.
Aducanumab

• Analyses of early-phase data on a promising monoclonal antibody, aducanumab (formerly BIIB037, Biogen Inc), in Alzheimer's disease (AD) show it appears to be effective regardless of apolipoprotein E (APOE) status and disease stage.
Anti-amyloid strategies – reducing production

• Another approach to reducing the amount of amyloid in the brain is to reduce the production

• Inhibiting the enzymes that help produce amyloid-beta will lead to less being produced

• BACE inhibitors specifically inhibit the beta-secretase enzyme involved in the amyloid cascade.
Anti-amyloid strategies – inhibiting aggregation

- **Curcumin** (a substance in the spice Turmeric) – has anti-oxidant, anti-inflammatory and anti-aggregation properties
- It binds beta-amyloid and reduces amyloid plaque burden in mice
- Phase 2 trial is ongoing – if effective – it may be a favoured therapy as toxicity is low
Far fewer drug trials have focussed on tau

Interest has grown recently because of difficulties with anti-A\(\beta\) treatments

Mouse and primate models of AD show amyloid plaques that respond to anti-amyloid therapy but these animal models don’t replicate the tau pathology seen in human AD

Aged dogs develop an AD-like disorder with amyloid and NFT’s

Treatment of these animals with anti-amyloid therapies reduces plaque load but doesn’t alter cognition or change tau pathology

There is a very robust correlation between tau pathology and clinical measures of dementia
Methylthioninium Chloride (Methylene Blue)

• First drug targeting tau
• Drug is derived from the dye used to stain NFT’s in neuropathological studies
• Primarily inhibits tau aggregation
• Phase 2 study showed cognitive benefits
• SPECT and FDG-PET results also encouraging
• Phase 3 trial for mild-moderate AD (both TQEH and RAH finished recruiting) will be finished February 2016
Other tau therapies

• Several other drugs that inhibit the development of tau have been studied

• **Observational studies** in geriatric patients taking chronic lithium for BPAD were found to have reduced risk of developing AD

• Lithium inhibits chemical changes in tau that leads to formation of NFT’s

• Studies on Lithium have been mixed – some have shown benefit with very low doses in mild cognitive impairment, others have shown worsening confusion – further studies are needed
Neurotransmitters and Receptors

• Serotonergic receptor in the brain is a promising drug target for Alzheimer’s Disease
• There is good evidence that this receptor is involved in memory and learning
• Some research suggests that these inflammatory processes are the underlying cause of AD and that it leads to Aβ and tau accumulation
• Large number of therapeutic trials of NSAID’s in AD (1993-2004) incl: Ibuprofen, indomethacin, naproxen, celecoxib ,rofécoxib and other anti – inflammatory meds such as prednisolone
• All were negative
Vitamins and Anti-oxidants

• In 2014 a group of Oxford University researchers assembled all the best clinical trial data involving 22,000 people and concluded that taking B vitamins and folate doesn’t slow mental decline as we age, nor is it likely to prevent AD

• Vitamin D – primarily has functions in bone health and metabolism but may also have anti-oxidant and anti-inflammatory properties

• not clear whether Vitamin D deficiency is causally related to cognition or is a marker for another process

• not confirmed that Vitamin D supplementation will have positive effect on cognition

• May work with two copies of Apo E 4
Vitamins and Anti-oxidants

- Vitamins E, C and beta-carotene (pre-cursor for Vitamin A) – all powerful anti-oxidants
- Multiple clinical trials provide evidence that supplements with these compounds did not alter cognitive outcomes in MCI, AD or healthy elderly but results still debated
- Ginkgo-biloba has been studied in trials
  - Reasonably firm evidence that it does not alter the risk of dementia or improve cognitive
- Omega-3 fatty acids found in fish oil and nuts – thought to be neuroprotective
  - Studies have failed to show any improvement in cognition in AD patients
  - In elderly without AD – inconclusive evidence that they may slow cognitive decline
- May take 2 ½ years before it is helpful
Mediterranean diet

• This diet is rich in fruits, vegetables, olive oil, legumes, whole grains and fish

• Studies have shown that people that closely follow a Mediterranean diet are less likely to have AD than those who don’t

• Research suggests that a Mediterranean diet may –
  -slow cognitive decline in older adults
  -reduce the risk of MCI progressing to AD
  -slow the progression of AD and prevent disease-related deaths
Diet in Alzheimer’s Disease

• A recent study looked at 3 different diets:

1. Mediterranean diet
2. DASH diet (designed to treat hypertension – low salt and sugar)
3. MIND diet (Combination of the above 2 diets)- emphasizes natural plant-based foods, limited saturated fats, encourages consumption of berries and green leafy vegetables (known to specifically benefit brain health)
Diet in Alzheimer’s Disease

• People that strictly followed any of these 3 diets had a lower risk of AD
• Even a modest adoption of the MIND diet approach such as eating 2 vegetable servings per week, 2 berry servings per week and one fish meal per week appeared to lower the risk of AD
• Researchers speculate that making healthy food choices may improve cholesterol and blood sugar levels and overall vessel health which may in turn reduce risk of MCI and AD
• Another theory is that a Mediterranean diet may help prevent brain tissue loss
• More studies are needed to know to what degree this diet prevents AD or slows cognitive decline
“Brain Training”

• This is quite broad and can include a range of structured mentally stimulating activities such as:
  ➢ crosswords
  ➢ learning a new language
  ➢ reading a book
  ➢ undertaking further education
  ➢ dedicated computerised brain training activities that focus on memory, attention or other cognitive functions

• Recent studies have found that “computerised brain training” is only modestly effective at improving cognitive performance in healthy older adults

• Further studies are about to start to see whether intensive computerised training can stop the progress of cognitive decline and the onset of dementia
Integrated Cognitive Stimulation and Training Program

• Integrated Cognitive Stimulation and Training Program (ICSTP) utilizing computer based programs, blended with paper and pencil exercises generally had positive effects on cognitive and memory functioning scores compared to a matched control group in individuals aged 65 years and above.

• These effects were sustained with no additional treatment after eight weeks.

• Statistically significant improvements of scores on the Dementia Rating Scale occurred for mildly and moderately impaired treatment participants.

• Slide 40
Brain Training Protects Against Cognitive Decline, Dementia

• A cognitive training program targeting speed of processing in healthy elderly adults cut the risk for dementia nearly in half over a 10-year period in the Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) study

• The speed training used in the ACTIVE study is available as an exercise called Double Decision. It is one of the exercises in BrainHQ [www.brainhq.com](http://www.brainhq.com), an online cognitive training program from Posit Science.
The stimulation electrodes are implanted chronically. DBS is an established therapeutic option in Parkinson’s disease, dystonia, and tremor. DBS has evolved to be one of the most effective treatments in Parkinson disease.

Deep transcranial magnetic stimulation (dTMS), already approved for treatment-resistant depression, is proving beneficial for obsessive compulsive disorder (OCD), adult attention-deficit/hyperactivity disorder (ADHD), and other psychiatric conditions, according to new research.
TMS

• Deep transcranial magnetic stimulation (dTMS), already approved for treatment-resistant depression, is proving beneficial for obsessive compulsive disorder (OCD), adult attention-deficit/hyperactivity disorder (ADHD), and other psychiatric conditions, according to new research.

• Patients with Alzheimer's disease (AD) who received repetitive transcranial magnetic stimulation (rTMS) to the prefrontal cortex experienced improved auditory sentence comprehension, results of a new study suggest. The improvement was apparent after 2 weeks and persisted for 8 weeks.

• It is likely that brain stimulation might interact with the intrinsic ability of the brain to restore damaged functions, by increasing the recruitment of compensatory functional networks and the plasticity of the system.
VNS was originally developed as a treatment for epilepsy. However, scientists noticed that it also had favorable effects on mood, especially depressive symptoms.

DBS has been studied as a treatment for depression or obsessive compulsive disorder (OCD).
Prolonging Remission in Depressed Elderly (PRIDE) study continue to support the use of right unilateral electrode placement and ultrabrief pulse stimuli as an optimal means of achieving a rapid response, and even remittance, within a week of delivering three courses of electroconvulsive therapy (ECT) in geriatric patients with major unipolar depression.

Neuronix’s neuroAD is already commercially available in Europe, Asia and Israel for slowing disease progression in mild to moderate Alzheimer cases.

The novel technology combines transcranial magnetic stimulation (TMS) and cognitive training of specific brain regions to slow the rate of mental deterioration in patients with mild to moderate Alzheimer’s and other neurodegenerative disorders. Study participants received the intervention daily for six weeks.
Tau Inhibitor Study Gets Mixed Reviews - timing

• A drug that inhibits tau aggregation significantly reduces disease progression in patients with mild to moderate Alzheimer's disease (AD), but only in those not already receiving standard therapy with AD medications, a new phase 3 study shows.

• AD treatments may eventually be "stage specific." In that scenario, an anti-tau drug may be given earlier, maybe during the prodromal stage of the disease, with standard treatments possibly introduced later
A Combo Therapy for Agitation in Alzheimer Disease

• Researchers from the Cleveland Clinic have published a preliminary 10-week randomized trial assessing the efficacy of dextromethorphan hydrobromide (Syrup is a combination of an antihistamine and a cough suppressant)/quinidine sulfate (Quinidine is an oral drug that’s used to treat and prevent irregular heart rate. Quinidine sulfate can also be used to treat malaria) in reducing agitation in patients with probable Alzheimer disease.

• 88% of the patients completed the study.

• The results showed significantly reduced measures of agitation, including occurrence and severity of symptoms.

• Patients treated with only dextromethorphan/quinidine had an average of 51% reduction in the measure of agitation from baseline to week 10 compared with a 26% reduction in those treated only with placebo.

• The rate of adverse events was relatively low but included falls, diarrhea, and urinary tract infections.
Insulin Resistance

• Insulin resistance and the way the brain processes insulin may be linked to AD

• Researchers are exploring the role of insulin in the brain and closely related questions of how brain cells use sugar and produce energy

• Researchers have been studying diabetic medications such as pioglitazone which also has potent anti-inflammatory effects
"Your green pills are all gone. Do you wanna take a blue and a yellow?"
• Targeting multiple disease-related proteins is an important new approach. If you think about what we are doing today, we are really targeting Alzheimer's disease with one target, one drug, and we see a potential for incremental benefit, but we are going to need a combination approach.

• All major diseases that have been successfully treated or cured have had a combination therapy approach. Alzheimer's is not going to be any different,
The Program!

- The 36-point program is personalized to each patient, based on test results that indicate what might be affecting the plasticity signaling network of that patient’s brain. Interventions are comprehensive and, for one patient, included:
  - Eliminating simple carbohydrates, gluten, and processed food from her diet
  - Adding yoga, meditation, and exercise
  - Increasing intake of fruits, vegetables, and fish
  - Sleeping 7 to 8 hours a night
  - Taking methylcobalamin, vitamin D3, fish oil, and CoQ10 each day and, at night, melatonin
  - Switching to an electric flosser and toothbrush
  - Reinstating hormone replacement therapy
  - Fasting 12 hours between dinner and breakfast and 3 hours between dinner and bedtime
  - Within 3 to 6 months after the program’s start, a participant and 8 other participants showed marked improvement that was sustained throughout the study, the longest patient follow-up lasting 2.5 years
<table>
<thead>
<tr>
<th>Patient</th>
<th>History, evaluation</th>
<th>Diagnosis</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>67F 3/3</td>
<td>2yr memory ?; FH+</td>
<td>aMCI</td>
<td>Normal x 2.5 yrs; working</td>
</tr>
<tr>
<td>69M 4/3</td>
<td>12yr memory ↓; FDG-PET+, NPsych+</td>
<td>Early AD</td>
<td>&quot;Clearly improved;&quot; working</td>
</tr>
<tr>
<td>70M 4/3</td>
<td>4yr memory ↓; NPsych+, failed MemTrax</td>
<td>AD</td>
<td>Improved; MemTrax passed</td>
</tr>
<tr>
<td>75M 3/3</td>
<td>1yr memory ↓</td>
<td>SCI</td>
<td>Improved; working</td>
</tr>
<tr>
<td>75F C677T</td>
<td>1yr memory ↓</td>
<td>aMCI/early AD</td>
<td>Improved</td>
</tr>
<tr>
<td>55F 3/3</td>
<td>4yr memory ↓</td>
<td>aMCI/early AD</td>
<td>Normal; working</td>
</tr>
<tr>
<td>72M 3/3</td>
<td>7yr memory ↓</td>
<td>aMCI</td>
<td>Improved; working</td>
</tr>
<tr>
<td>55M 4/3</td>
<td>2yr memory ↓</td>
<td>SCI</td>
<td>Normal; working</td>
</tr>
<tr>
<td>63F 4/3</td>
<td>FH dementia, mild memory ↓</td>
<td>SCI</td>
<td>Normal, negative amyloid PET; working</td>
</tr>
<tr>
<td>60F 4/3</td>
<td>4yr rapid decline; MoCA 6, amyloid PET+</td>
<td>Late AD</td>
<td>Decline</td>
</tr>
</tbody>
</table>
Assessment

Sensory Memory
- Sight
- Smell
- Sound
- Taste
- Touch

Short-Term Memory
- Attention
- Rehearsal
- Elaboration and Organization

Long-Term Memory
- Retrieval

Lost Lost
Assessment

Cognitive tests

Behavior

History

Neuro exam

Objective tests
Dementia Work-Up

• H&P
• **Objective** cognitive measurement (Computer Testing)
• Diagnostics
  • Labs
  • Imaging ?
  • More specific testing (e.g., neuropsychometric)?
• Diagnosis
• **Family/Community member** meeting
New Checklist Tests Behavior Change as First Sign of Dementia (MBI-C)

• Mild behavioral impairment (MBI), not memory woes, may be the first sign of mild cognitive impairment (MCI) or dementia

• MBI is defined as a syndrome of neuropsychiatric symptoms (NPS) that start later in life and are sustained for at least 6 months.

• Not a blip in behavior or reacting to a loss, but a real, meaningful change in behavior

• Evidence shows that older adults with normal cognition and neuropsychiatric symptoms are more likely to become cognitively impaired and develop MCI than are people without neuropsychiatric symptoms
Mild Behavioral Impairment Checklist (MBI-C)

Date:  
Rated by:  
☐ Clinician  
☐ Informant  
☐ Subject  
Location:  
☐ Clinic  
☐ Research  
Label

Circle “Yes” only if the behavior has been present for at least 6 months (continuously, or on and off) and is a change from her/his longstanding pattern of behavior. Otherwise, circle “No”.

Please rate severity: 1 = Mild (noticeable, but not a significant change); 2 = Moderate (significant, but not a dramatic change); 3 = Severe (very marked or prominent, a dramatic change). If more than 1 item in a question, rate the most severe.

<table>
<thead>
<tr>
<th>This domain describes interest, motivation, and drive</th>
<th>YES</th>
<th>NO</th>
<th>SEVERITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Has the person lost interest in friends, family, or home activities?</td>
<td>Yes</td>
<td>No</td>
<td>1 2 3</td>
</tr>
<tr>
<td>Does the person lack curiosity in topics that would usually have attracted her/his interest?</td>
<td>Yes</td>
<td>No</td>
<td>1 2 3</td>
</tr>
<tr>
<td>Has the person become less spontaneous and active – for example, is she/he less likely to initiate or maintain conversation?</td>
<td>Yes</td>
<td>No</td>
<td>1 2 3</td>
</tr>
<tr>
<td>Has the person lost motivation to act on her/his obligations or interests?</td>
<td>Yes</td>
<td>No</td>
<td>1 2 3</td>
</tr>
<tr>
<td>Is the person less affectionate and/or lacking in emotions when compared to her/his usual self?</td>
<td>Yes</td>
<td>No</td>
<td>1 2 3</td>
</tr>
<tr>
<td>Does she/he no longer care about anything?</td>
<td>Yes</td>
<td>No</td>
<td>1 2 3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>This domain describes mood or anxiety symptoms</th>
<th>YES</th>
<th>NO</th>
<th>SEVERITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Has the person developed sadness or appear to be in low spirits? Does she/she have episodes of tearfulness?</td>
<td>Yes</td>
<td>No</td>
<td>1 2 3</td>
</tr>
<tr>
<td>Has the person become less able to experience pleasure?</td>
<td>Yes</td>
<td>No</td>
<td>1 2 3</td>
</tr>
<tr>
<td>Has the person become discouraged about their future or feel that she/he is a failure?</td>
<td>Yes</td>
<td>No</td>
<td>1 2 3</td>
</tr>
<tr>
<td>Does the person view herself/himself as a burden to family?</td>
<td>Yes</td>
<td>No</td>
<td>1 2 3</td>
</tr>
<tr>
<td>Question</td>
<td>Yes</td>
<td>No</td>
<td>1</td>
</tr>
<tr>
<td>-------------------------------------------------------------------------</td>
<td>-----</td>
<td>----</td>
<td>----</td>
</tr>
<tr>
<td>Has the person become more easily frustrated or impatient? Does she/he have troubles coping with delays, or waiting for events or for their turn?</td>
<td>Yes</td>
<td>No</td>
<td>1</td>
</tr>
<tr>
<td>Does the person display a new recklessness or lack of judgement when driving (e.g. speeding, erratic swerving, abrupt lane changes, etc.)?</td>
<td>Yes</td>
<td>No</td>
<td>1</td>
</tr>
<tr>
<td>Has the person become more stubborn or rigid, i.e., uncharacteristically insistent on having their way, or unwilling/unable to see/hear other views?</td>
<td>Yes</td>
<td>No</td>
<td>1</td>
</tr>
<tr>
<td>Is there a change in eating behaviors (e.g., overeating, cramming the mouth, insistent on eating only specific foods, or eating the food in exactly the same order)?</td>
<td>Yes</td>
<td>No</td>
<td>1</td>
</tr>
<tr>
<td>Does the person no longer find food tasteful or enjoyable? Are they eating less?</td>
<td>Yes</td>
<td>No</td>
<td>1</td>
</tr>
<tr>
<td>Does the person hoard objects when she/he did not do so before?</td>
<td>Yes</td>
<td>No</td>
<td>1</td>
</tr>
<tr>
<td>Has the person developed simple repetitive behaviors or compulsions?</td>
<td>Yes</td>
<td>No</td>
<td>1</td>
</tr>
<tr>
<td>Has the person recently developed trouble regulating smoking, alcohol, drug intake or gambling, or started shoplifting?</td>
<td>Yes</td>
<td>No</td>
<td>1</td>
</tr>
<tr>
<td><strong>This domain describes following societal norms and having social graces, tact, and empathy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Has the person become less concerned about how her/his words or actions affect others? Has she/he become insensitive to others’ feelings?</td>
<td>Yes</td>
<td>No</td>
<td>1</td>
</tr>
<tr>
<td>Has the person started talking openly about very personal or private matters not usually discussed in public?</td>
<td>Yes</td>
<td>No</td>
<td>1</td>
</tr>
<tr>
<td>Does the person say rude or crude things or make lewd sexual remarks that she/he would not have said before?</td>
<td>Yes</td>
<td>No</td>
<td>1</td>
</tr>
</tbody>
</table>
University of Pennsylvania Smell Identification Test (UPSIT)

- Clearly, odor identification impairment is an early sign of Alzheimer's disease and can be used to supplement a diagnostic workup.

- The UPSIT involves scratching a surface, sniffing the odor that's released, and identifying it from a multiple-choice list. The test is scored from 0 (no correct answer) to 40 (all answers correct).

- A low score indicates a decreased ability to correctly identify odors.

- The loss of odor identification, which is based on memory, is not the same as an impaired sense of smell.

- The sense of smell does get impaired in AD, but not until much later in the disease.

- The full UPSIT, which takes about 20 minutes to complete.

- There are many false-positives in, for example, heavy smokers, those with a respiratory infection, and those with certain other conditions.
MMSE vs. MoCA

• Both stage AD as mild, moderate, or severe

  ▪ MoCA emerging as the preferred brief assessment tool
    ▪ Superior sensitivity in detecting mild cognitive impairment
    ▪ Increased sensitivity to executive & language dysfunction

  ▪ Sensitivity and Specificity (%) MoCA and MMSE:

<table>
<thead>
<tr>
<th>Group (n)</th>
<th>≥ 26</th>
<th>&lt; 26</th>
<th>&lt; 26</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal controls (90)</td>
<td>87</td>
<td>90</td>
<td>100</td>
</tr>
<tr>
<td>Mild Cognitive Impairment (94)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alzheimer’s Disease (93)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MoCA</td>
<td>100</td>
<td>18</td>
<td>78</td>
</tr>
<tr>
<td>MMSE</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Screening Tool Selection

Montreal Cognitive Assessment (MoCA)
• Sensitivity: 90% for MCI, 100% for dementia
• Specificity: 87%

St. Louis University Mental Status (SLUMS)
• Sensitivity: 92% for MCI, 100% for dementia
• Specificity: 81%

Mini-Mental Status Exam (MMSE)
• Sensitivity: 18% for MCI, 78% for dementia
• Specificity: 100%

Larner 2012; Nasreddine et al., 2005; Tariq et al., 2006; Ismail et al., 2010
## MoCA Scoring: Sam

### Memory
- Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.

<table>
<thead>
<tr>
<th></th>
<th>FACE</th>
<th>VELVET</th>
<th>CHURCH</th>
<th>DAISY</th>
<th>RED</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st trial</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>2nd trial</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
</tbody>
</table>

No points

### Attention
- Read list of digits (1 digit/sec).
- Subject has to repeat them in the forward order
- Subject has to repeat them in the backward order

<p>| | | | | | |</p>
<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1st trial</td>
<td>✔ 2 1 8 5 4</td>
<td>✔ 7 4 2</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2/2

- Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors

<p>| | | | | | |</p>
<table>
<thead>
<tr>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>FBACMNAAJKLBFAKDEAAAJAMOFABB</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

0/1

- Serial 7 subtraction starting at 100

<p>| | | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>93</td>
<td>86</td>
<td>79</td>
<td>72</td>
<td>64</td>
<td>65</td>
</tr>
</tbody>
</table>

4 or 5 correct subtractions: 3 pts, 2 or 3 correct: 2 pts, 1 correct: 1 pt, 0 correct: 0 pt

2/3

### Language
- Repeat: I only know that John is the one to help today. ✔
- The cat always hid under the couch when dogs were in the room. ✔

2/2

- Fluency / Name maximum number of words in one minute that begin with the letter F

[✓] 18 (N ≥ 11 words)

1/1

### Abstraction
- Similarity between e.g. banana - orange = fruit
- train - bicycle [✓] watch - ruler

1/2

### Delayed Recall
- Has to recall words WITH NO CUE

<table>
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<tr>
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<th>CHURCH</th>
<th>DAISY</th>
<th>RED</th>
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</thead>
<tbody>
<tr>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
</tbody>
</table>

Points for UNICUED recall only

0/1

### Optional
- Category cue
- Multiple choice cue

### Orientation
- [✓] Date
- [✓] Month
- [✓] Year
- [✓] Day
- [✓] Place
- [✓] City

6/6

© Z. Nasreddine MD
www.mocatest.org

Administered by: Dr. Barley

TOTAL 21/30

Normal: ≥26 / 30

Add 1 point if ≤ 12 yr edad
Diagnosis – Based on data

- Rule out reversible causes B12, thyroid, Vitamin D, NPH etc.
- Alzheimer's patients taking both cholinesterase inhibitors and anticholinergic medications, may have no benefits as these two drugs antagonize each other, and neither will work
- Medications with strong anticholinergic side effects are well known for causing cognitive impairment in AD patients
- Rule out delirium
  - Minor Neurocognitive Disorder - 1-2 SD < mean, 0.5 SD decline from patient’s baseline
  - Major Neurocognitive Disorder - > 2 SD below mean
  - Due to what??????????????????
National Institute on Aging (NIA) have issued the first new criteria and guidelines to diagnose Alzheimer's disease in 27 years

• New stages

• **Stage 1** — asymptomatic cerebral amyloidosis;

• **Stage 2** — amyloidosis plus evidence of "downstream" neurodegeneration; and

• **Stage 3** — amyloidosis, neuronal injury, plus subtle cognitive/behavioral decline.
National Institute on Aging (NIA) have issued the criteria and guidelines to diagnose Alzheimer's disease.
Treatment

• Look for co-morbid, apnea, depression, infections, sleep problems etc.
• Treat co morbid
• Avoid unnecessary drugs.. Do not medicate staff anxiety
• End stage think hospice
• Use it or lose it - Use it and improve it (function)
• Avoid excess disability
Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo.
Acetylcholinesterase

• Drugs that prevent the breakdown of acetylcholine, a brain chemical involved in memory & other functions related to thinking
  ▪ ↑ acetylcholine = ↑ cognitive abilities

• FDA-approved medications*
  ▪ Donepezil (Aricept)
  ▪ Galantamine (Razadyne)
  ▪ Rivastigmine (Exelon)

*Tacrine, the first cholinesterase inhibitor approved in 1993, is rarely used now due to its potential to cause liver damage
AChEIs

• All approved for **mild-moderate** Alzheimer’s disease

• Donepezil and Rivastigmine patch approved for **severe** disease

• Most common side effects are gastrointestinal
  ▪ Nausea / Vomiting / Diarrhea / Abdominal Cramping

• Side effects may become more tolerable over a few weeks. Can improve tolerability with:
  ▪ Slow titration
  ▪ Administration with food
Normal Brain Cells

Neurotransmitters (AChE)- being sent - message being communicated to the next cell
Once the message is sent, then enzymes lock onto the messenger chemicals and take them out of circulation so a new message can be sent.
Brain Cells with Alzheimer’s

- Plaques
- Tangles
- Less neurotransmitter
- Further to go to get to the next cell

Enzymes (AChE inhibitors) – get to them BEFORE they deliver their message
Alzheimer's drugs provide FAKE messenger chemicals that distract the enzymes. They attach to the Fake AChE & the message can get thru.

What do Alzheimer’s drugs DO?

Aricept, Exelon, Razadyne
Donepezil (Aricept®)

• Once-daily dosing at bedtime
  ▪ Brand: 5 mg, 10 mg, & 23 mg tablet
  ▪ Generic: 5 mg & 10 mg tablet
  ▪ Also supplied in an ODT form (5 mg & 10 mg)

• Dose: 5 mg daily x 4 weeks, may ↑ to 10 mg daily after 4-6 weeks
  ▪ Patients should be on 10 mg daily for ≥ 3 months before starting the 23 mg tablet
  ▪ Marginal improvement compared to 10 mg/day dose
For Patients With Dementia: To E or Not to

• Vitamin E (alpha-tocopherol) stands out as having the greatest evidence for possible benefit in slowing down the progression of AD and other forms of dementia.

• Vitamin E is an antioxidant and may mitigate the oxidative stress that is thought to contribute to the neuropathology of AD.

• Vitamin E has been shown by large randomized controlled studies to decrease the rate of progression of AD in people with mild to moderate disease.

• However, the magnitude of this effect is very modest and may not be clinically noticeable.

• In addition, high-dose vitamin E should be recommended with caution in patients with increased risk for bleeding and those with known coronary heart disease or congestive heart failure. Vitamin E supplementation has no role in the prevention of dementia.
Rivastigmine (Exelon®)

- Capsules (twice-daily dosing)
  - 1.5 mg, 3 mg, 4.5 mg, & 6 mg (brand & generic)
  - Initially, 1.5 mg PO BID w/ food, can ↑ by 3 mg/day increments after ≥ 2 weeks of treatment
- Oral Solution
- Transdermal patch (per 24 hours)
  - 4.6 mg, 9.5 mg, 13.3 mg (brand only)
  - Initially 4.6 mg once daily, can ↑ to 9.5 mg and then 13.3 mg after ≥ 4 week intervals

- MDD = 12 mg (6 mg PO BID) or one patch delivering 13.3 mg per 24 hours once daily
Galantamine (Razadyne®)

• Similar efficacy to donepezil but may have increased GI side effects
  ▪ Counsel patients to take with food
  ▪ Maintain adequate hydration

• Prevents breakdown of ACh and works by stimulating nicotinic receptors in the brain
  ▪ Improves nicotinic transmission and increases release of more ACh

NMDA Antagonist: Memantine

• N-methyl-D-aspartate (NMDA) receptor antagonist

• Modifies function of NMDA brain receptor to ↓ the negative effect of having too much exposure to the brain chemical glutamate

• ↑ glutamate = ↑ death of nerve cells which can worsen memory loss

• Appears to be neuroprotective
Combination Regimens

- The combination of an AChEI and memantine can be used in advanced disease or if the person does not respond to an AChEI by itself
  - Evidence (and its interpretation) of adding memantine to acetylcholinesterase inhibitors is mixed

- Namzaric, a fixed-dose combination of extended-release memantine and donepezil approved in December 2014
  - Two strengths: 28/10 mg and 14/10 mg
  - Indicated for treatment of mild-moderate AD in patients already taking the two drugs
• Plasticity – *the ability to be moulded /shaped* (from Greek ”plastos”)

• Preventing ‘excess’ or unnecessary disability
  ► Making the most of remaining ability
  ► Managing impact of cognitive impairment
  ► Improving social context and emotional coping
Activity Therapy

• The more meaningful your activity program is to the resident, the less negative behavior you will and the residents will function better
- Sensory training
- Inability to interact with the environment.
- Not oriented to themselves
- Repetitive exercises

- Reality Orientation
  Used with the moderately confused or those at risk to be confused.
  Consistent, accurate information

- Remotivation
  Start to reuse communication skills in-group
  Structured five step procedure

- Reminiscing
  Client remembers forgotten incidences and strives to communicate and recapture emotions
  Trained listener

- Other approaches and therapies
  Advanced Remotivation
  Resocialization,
  Integrated Cognitive Stimulation, DBT, CBT, Stress management

- Validation Therapy

Very much for the WELL
## Non-pharmacological intervention to Alzheimer patients

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Cognitive</th>
<th>ADL</th>
<th>BPSD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive training</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Cognitive rehabilitation</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Cognitive stimulation therapy</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Snoezelen/multisensory stimulation</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Reality orientation</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Reminiscence therapy</td>
<td>+</td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td>Validation therapy</td>
<td>+</td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td>Physical activity</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Light therapy</td>
<td>+</td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td>Music therapy</td>
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<td>−</td>
<td>+</td>
</tr>
<tr>
<td>Aromatherapy</td>
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<td>−</td>
<td>+</td>
</tr>
<tr>
<td>Animal-assisted therapy</td>
<td>−</td>
<td>−</td>
<td>+</td>
</tr>
</tbody>
</table>

1. ADL, activities of daily living; BPSD, behavioral and psychological symptoms of dementia.
THE END