MAJOR NEUROCOGNITIVE DISORDER DUE TO ALZHEIMER’S DISEASE
Disclosure

- CCTA #0001 Rivistagmine Patch in Veterans with Cognitive Impairment Following TBI.
- Vitamin E and Memantine in Alzheimer’s Disease/CSP 546 study
Content

- Definition
- Prevalence
- Neuropathology
- Risk Factors
- Pathophysiology - Biomarkers
- Clinical Presentation
- Medicare Annual Wellness Visit
- Diagnosis
- Progression
- Treatments
- Conclusions
A. Evidence of significant cognitive decline from a previous level of performance in one or more area of cognitive domains (complex attention, executive function, learning and memory, language, perceptual-motor or social cognition) based on:

1. Concern of the individual, a knowledgeable informant or the clinician that there has been a significant decline in cognitive function; and

2. substantial impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment.

B. The cognitive deficits interfere with independence in everyday activities.

C. The cognitive deficits do not occur exclusively in the context of a delirium.

D. The cognitive deficits are not better explained by another mental disorder (e.g., major depressive disorder, schizophrenia).
Major neurocognitive disorder  DSM- V
Domains

- Complex attention: patient has increased difficulty in environments with multiple stimuli (TV, radio, conversation). Has difficulty holding new information in mind (recalling phone numbers, or addresses just given or reporting what was just said).
- Executive function: patient is not able to perform complex projects. Needs to rely on others to plan instrumental activities of daily living or make decisions.
- Learning and memory: patient repeats self in conversation, often within the same conversation. Cannot keep track of short list of items when shopping or of plans for the day. Requires frequent reminders to orient task in hand.
- Language: patient has significant difficulties with expressive or receptive language. Often uses general terms such as “that thing” and “you know what I mean”. With severe impairment may not even recall names of closer friends and family.
- Perceptual – Motor: Has significant difficulties with previously familiar activities (using tools, driving motor vehicle), navigating in familiar environments.
- Social cognition: patient may change changes in behavior (shows insensitivity to social standards). Makes decisions without regard to safety. Patient usually has little insight into these changes.
Major neurocognitive disorder due to Alzheimer’s Disease

A. the criteria are met for major neurocognitive disorder.

B. There is insidious onset and gradual progression of impairment in one or more cognitive domains.

C. Criteria are met for either probable or possible Alzheimer’s disease as follows:
   For major neurocognitive disorder probable Alzheimer’s disease is diagnosed if either of the following is present; otherwise, possible Alzheimer’s disease should be diagnosed.

1. Evidence of a causative Alzheimer’s disease genetic mutation from family history or genetic testing.

2. All 3 of the following are present:
   a. Clear evidence of decline in memory and learning and at least one other cognitive domain (based on detailed history or serial neuropsychological testing).
   b. Steadily progressive, gradual decline in cognition, without extended plateaus.
   c. No evidence of mixed etiology (i.e., absence of other neurodegenerative or cerebrovascular disease or another neurological, mental or systemic disease likely contributing to cognitive decline).
Prevalence

- Age 65 prevalence is 1%.
- At age 80 the prevalence is around 15%.
- At age 90 the prevalence may be as high as 40%.
- Alzheimer’s disease accounts for between 50% and 70% of all cases of dementia.
Prevalence of Alzheimer’s Dementia

- 2013: 5 million Americans older than 65 have Alzheimer’s dementia.
- 2025: 7.1 million of Americans older than 65 will have Alzheimer’s dementia.
Neuropathology of Alzheimer’s Disease

- Senile Plaques: extracellular deposits of Beta Amyloid, dentrites and glial cells.
- Neurofibrillary tangles: intracellular accumulation of tau and ubiquitin proteins.
- Early neuronal loss: especially in the hippocampus.
- Of note the pathology of AD may be found in cognitively normal patients, patients with MCI and patients with Dementia.
Senile Plaques

FIGURE 1

ALZHEIMER DISEASE UPDATE.
Matthew, Brandy
CONTINUUM: Lifelong Learning in Neurology, 16(2),
Dementia 15-30, April 2010.
DOI: 10.1210/01.CDN.0000358/110.41691.4a

FIGURE 1-2 Nerotic plaques demonstrated by silver
cast on cortex of patient with Alzheimer
disease. Figure courtesy of Bernardino Ghetti, MD,
Indiana University School of Medicine.
Neurofibrillary tangles
Neuronal Loss
Risk factors for Alzheimer’s Dementia

- #1 Risk factor is advancing age.
- #2 Risk factor is family history of dementia.
# Genetic Risk factors

## APOE 4
- 20% of cases of Late Onset AD related with APOE4
- APOE alleles are on chromosome 19
- APOE4 alleles play a role in Cholesterol transportation
- 1 copy of APOE4 increases the risk of acquiring AD 3 times
- 2 copies of APOE4 increases the risk 5 times

## Autosomal Dominant
- 3 genes identified with Autosomal Dominant mutation. (2% of cases of AD) with abnormal production of amyloid β
  - #1 Presenilin 1, mutation on chromosome 14.
  - #2APP mutation (Amyloid Precursor Protein), chromosome 21.
  - #3Presenilin 2, mutation on chromosome 1.

## Down Syndrome
- Trisomy 21
- 3 copies of APP (Amyloid Precursor Protein)
Environmental Risk Factors

**Early to mid life factors**
- Head injury
- Obesity
- Insulin resistance
- Vascular risk factors like: HTN, hyperlipidemia.
- OSA

**Mid to late life factors**
- Individuals with isolated lifestyles are more apt to develop cognitive decline with aging.
- Late life depression (there is the question if depression is a prodromal of AD)
- MCI (Minor Neurocognitive Disorder)
Pathophysiology of AD

Hypothetical model of AD pathophysiological cascade

- Age
- Genetics
- Cerebrovascular risk factors
- Other age-related brain diseases

Amyloid-β Accumulation

Synaptic Dysfunction
- Glial Activation
- Tangle Formation
- Neuronal Death

Cognitive Decline

Brain and cognitive reserve
- ? Environmental factors

Reisa A Sperling et al. Alzheimer’s & Dementia 7 (2011) 280-292
Pathophysiology of AD

Appearance of Plaques vs. Dementia

- Amyloid Plaques at Autopsy
- Prevalence of AD Dementia

Percent positive (%)

Age (years)

## Biomarkers in Alzheimer’s Disease

### Brain amyloid-Beta (Aβ) protein deposition

- Low CSF Aβ42.
- Positive PET amyloid imaging.

### Neuronal Degeneration

- Elevated CSF tau.
- Decreased Fluorodeoxyglucose (FDG) uptake on PET in temporoparietal cortex.
- Disproportionate atrophy on structural MRI in medial basal and lateral temporal lobe, and medialparietal cortex.
In persons who meet the core criteria for probable AD dementia the biomarker evidence may increase the certainty that the basis of the clinical dementia syndrome is the AD pathophysiological process.

However the National Institute of Aging-Alzheimer’s Association Workgroups do not advocate the use of AD biomarkers for routine diagnostic purposes at current time:

1. The core clinical criteria provide a good diagnostic accuracy and utility in most patients’
2. More research needs to be done to ensure the appropriate criteria is used with the biomarkers.
3. Limited standardization of biomarkers.
4. Access to biomarkers is limited in community settings.
10 Early sings and symptoms of Alzheimer’s dementia

- Memory loss that disrupts daily life.
- Challenges in planning or solving problems.
- Difficulty completing familiar tasks at home, at work or at leisure.
- Confusion with time or place.
- Trouble understanding visual images and spatial relationships.
- New problems with words in speaking or writing.
- Misplacing things and losing the ability to retrace steps.
- Decreased or poor judgment.
- Withdrawal from work or social activities.
- Changes in mood and personality.
The goal is to detect during the primary care visit the patients with high likelihood of having dementia.

“Have you noticed any changes in your memory or ability to complete routine tasks, such as paying bills or preparing a meal?”
Instrument for Office-Based Assessments

- Memory Impairment Screen (MIS)
- General Practitioner Assessment of Cognition (GPCOG)
- Mini-Cog
- MoCA, Folstein MMSE
Diagnosis

Diagnose Dementia

- A. Subjective cognitive complaints.
- B. Dysfunction (IADL’s and ADL’s).
- C. Objective cognitive deficits.

Etiology

- Physical and neurological examination
- Diagnostic laboratories
- Neuroimaging
Testing Recommendations in the Diagnosis of Major Neurocognitive Disorder

- Screening for Depression
- Screening for Thyroid function
- Screening for B12 and Folate
- Structural neuroimaging with MRI or non contrast CT scan
- Syphilis screening / HIV
- Neuropsychological testing
Physical and Neurological Examination

- In mild to moderate dementia NE is unremarkable.
- Later in the illness patients may develop Pyramidal signs, hypereflexia, Parkinsonism.
- Dysphagia is an important late symptom of the disease and is a contributing factor to most AD deaths resulting from aspiration pneumonia.
Clinical Neuroimaging

- Structural imaging in early dementia may appear normal or with no specific atrophy.
- MRI: atrophy of the hippocampus and parahippocampal gyrus, cingulated gyrus, dilated lateral ventricles.
- PET/SPECT: decreased metabolism in parietal and temporal association cortices (research).
Progression

- Gradual slow progression.
- 10 years average from diagnosis to death.
- Memory impairment appears early in the course.
- It can also present behavioral symptoms like hallucinations, delusions, depression, apathy, agitation, aggression, pacing, wandering, sleep disturbances.
- Death often occurs from aspiration pneumonia.
## Major Neurocognitive Disorder; Mild Severity

<table>
<thead>
<tr>
<th>Clinical Presentation</th>
<th>Approximate MMSE</th>
<th>Emotional impact</th>
<th>Impact on family</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Decrease knowledge on current events.</td>
<td><strong>20</strong></td>
<td>• Denial</td>
<td>• Family takes over finances and similar responsibilities.</td>
</tr>
<tr>
<td>• Concentration deficits.</td>
<td></td>
<td>• Emotional withdrawal</td>
<td>• Family Begins to supervise patient.</td>
</tr>
<tr>
<td>• Decrease ability to travel, handle finances.</td>
<td></td>
<td></td>
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<tr>
<td>• Inability to perform complex tasks.</td>
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<td></td>
</tr>
<tr>
<td>• Denial</td>
<td></td>
<td></td>
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<td>• Emotional withdrawal</td>
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<tr>
<td>• Family Begins to supervise patient.</td>
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</table>
# Major Neurocognitive Disorder; Moderate Severity

## Clinical Presentation

- May forget name of spouse, on whom they are entirely dependent.
- Unaware of all recent events and experiences in their life.
- Will become incontinent.
- Needs assistance with some ADL’s.
- Recalls on own name.
- Continues to distinguish familiar from unfamiliar persons.

## Approximate MMSE

| 15-5 |

## Emotional impact

- Occasional tearfulness and anger
- Delusional behavior.
- Anxiety symptoms.
- Agitation.
- Aggressive behavior.
- Wandering, pacing, storing or hiding objects.

## Impact on family

- Spouse or caregiver is frequently forced to his/her life to patient 24/7.
- Emotional burden becomes unbearable.
- Institutionalization is considered.
Major Neurocognitive Disorder; Severe Severity

<table>
<thead>
<tr>
<th>Clinical Presentation</th>
<th>Approximate MMSE</th>
<th>Emotional impact</th>
<th>Impact on family</th>
</tr>
</thead>
<tbody>
<tr>
<td>All verbal abilities are lost.</td>
<td>&lt; 5</td>
<td>Screams and other verbal outburst, babbling become means of communication.</td>
<td>Most families institutionalize their beloved spouse or parent in the evolution of this stage.</td>
</tr>
<tr>
<td>Dependent in all ADL's</td>
<td></td>
<td>Pathological passivity.</td>
<td></td>
</tr>
<tr>
<td>Need assistance with toileting, feeding.</td>
<td></td>
<td></td>
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<tr>
<td>Basic psychomotor skills (walking) are lost with the progression of this stage.</td>
<td></td>
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<tr>
<td>Can develop generalized rigidity.</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Prevention on decubitus ulcers, aspiration and contractures are major issues in care</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Treatment

<table>
<thead>
<tr>
<th>Mechanism of action</th>
<th>Donepezil</th>
<th>Galantamine</th>
<th>Rivastigmine (oral)</th>
<th>Rivastigmine (transdermal)</th>
<th>Memantine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholinest. I</td>
<td>PO 5mg/10mg /23mg/day</td>
<td>PO 4mg BID/12mg BID</td>
<td>PO 1.5mgBID/6mg BID</td>
<td>Transdermal 4.6mg QD/9.5mg QD</td>
<td>PO 5mgQD/10mg BID</td>
</tr>
</tbody>
</table>

| Absorption affected by food | No | Yes | Yes | Affected site patch admistration | No |

| Hours to maximum serum concentration | 3-5 | 0.5-1.0 | 0.5-2.0 | 8-10 | 3-7 |

| Serum half life (hours) | 70-80 | 5-7 | 2-8 | 3-4 (after patch removed) | 60-80 |

| Protein binding | 96% | 18% | 40% | 45% |

| Cit P 450 | Substrate of CYP 2D6, 3A4 | Substrate of CYP 2D6, 3A4 | None | None |
Cholinesterase Inhibitors

- Modest Benefits.
- Reduce deterioration of the illness
- Benefits are symptomatic, not disease modifying.
- Primary benefits on cognition and IADL’s.
- Also improvement in symptoms of depression, agitation, anxiety and apathy.
- No difference in benefits among Ache I.
Memantine (Namenda)

- N-Methyl-D Aspartate (NMDA) antagonist.
- Improves cognition modestly.
- Regulates excessive glutamate activity.
- Indication: moderate to severe dementia.
- Benefits are symptomatic, not disease modifying.
- Reduce deterioration of the illness.
- Adverse effects: agitation, dizziness, confusion, headache, hallucinations
Caprylidene (Axona)

- “Medical food”
- In AD neurons are less able to use glucose as energy source.
- Axona increases ketones in brain.
- Ketones provide alternative energy to neurons with compromised glucose metabolism.
- FDA approved for Mild AD
- Prescription only: comes in a powder.
- It has GI side effects, may increase BUN, uric acid, creatinine.
## AD Investigational Treatment Strategies

<table>
<thead>
<tr>
<th>Aβ Related</th>
<th>Tau Related</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amyloid antiaggregation</td>
<td>Tau antiaggregation</td>
<td>Antioxidative</td>
</tr>
<tr>
<td>Direct Aβ binding</td>
<td></td>
<td>Mitochondrial stabilizer</td>
</tr>
<tr>
<td>Receptor for advanced glycation end products (RAGE) inhibitor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aβ immunotherapy</td>
<td>Microtubule stabilizer</td>
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<tr>
<td>Polyclonal antibodies</td>
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<td></td>
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<tr>
<td>Monoclonal antibodies</td>
<td></td>
<td>Hormone modulation</td>
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<tr>
<td>Active vaccination</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secretase modulation</td>
<td></td>
<td></td>
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<tr>
<td>γ-Secretase inhibition</td>
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*Continuum Lifelong Learning Neurol 2010;16(2)*
### Non-Pharmacological Psychosocial Treatments in AD

<table>
<thead>
<tr>
<th>Category</th>
<th>Treatments</th>
</tr>
</thead>
</table>
| **Stimulation Oriented**     | - Recreational therapy  
                             | - Art therapy  
                             | - Pet therapy  
                             | - Exercise therapy |
| **Emotion Oriented**         | - Supportive therapy  
                             | - Reminiscence therapy |
| **Cognition Oriented**       | - Cognitive Rehabilitation and retraining. Better for patients with stable deficits (like stroke). |
Senior Day Program Activities

- Indicated for mild-mod severity
- Structure group activities
- Stimulation-oriented therapies: exercise, craft, pet therapies
- Social work counseling
- Guest speakers invited, trips taken
Caregiver interventions

- High rate of caregiver burnout and depression.
- Respite care for patient and caregiver
- Counsel caregiver, progression of the illness
- Provide sources of support
- Encourage involvement of other family members
- Information regarding NH placement
- Recommend financial and legal planning
Conclusion

- By DSMV the term Alzheimer’s dementia = Major Cognitive Disorder due to Alzheimer’s Disease.
- Alzheimer’s disease accounts for between 50% and 70% of all cases of dementia.
- 2025: 7.1 million of Americans older than 65 will have Alzheimer’s dementia.
- The pathology of Alzheimer’s Disease (senile plaques, neurofibrillary tangles, early neuronal) loss may be found in cognitively normal patients, patients with MCI and patients with Dementia.
- The structured cognitive assessment tools recommended for AWV: Memory Impairment Screen (MIS), General Practitioner Assessment of Cognition (GPCOG), Mini-Cog, Short IQCODE, AD8 and GPCOG. All of this assessments are free – online.
- The National Institute of Aging-Alzheimer’s Association Workgroups do not advocate the use of AD biomarkers for routine diagnostic purposes at current time.
References

- Cyndy B. Cordell et al. Alzheimer’s Association recommendations for operationalizing the detection of cognitive impairment during the Medicare Annual Wellness Visit in Primary Care setting. Alzheimer’s &Dementia (2013) 1-10.
- Diagnostic Criteria from DSM- V.
THANK YOU
Stage 1
Asymptomatic amyloidosis
- High PET amyloid tracer retention
- Low CSF Aβ₁₋₄₂

Stage 2
Amyloidosis + Neurodegeneration
- Neuronal dysfunction on FDG-PET/fMRI
- High CSF tau/p-tau
- Cortical thinning/Hippocampal atrophy on sMRI

Stage 3
Amyloidosis + Neurodegeneration + Subtle Cognitive Decline
- Evidence of subtle change from baseline level of cognition
- Poor performance on more challenging cognitive tests
- Does not yet meet criteria for MCI

MCI → AD dementia
Alzheimer’s Disease is not synonymous with dementia of the Alzheimer’s type (DAT).

The 2011 criteria expand the definition of Alzheimer’s Disease to include an asymptomatic (preclinical phase); a symptomatic (pre-dementia phase) and a dementia phase.
Dementia Definition

- Dementia is diagnosed when there are cognitive or behavioral symptoms that:
  - 1. Interfere with the ability to function.
  - 2. Represent a decline from previous levels of function.
  - 3. Are not explained by delirium or a major psychiatric disorder.
  - 4. Cognitive impairment is diagnosed by information from patient or family and by objective cognitive assessment.
  - 5. The cognitive or behavioral impairment involves a minimum of 2 domains:
    - A. Impaired ability to acquire and remember new information.
    - B. Impaired reasoning and handling of complex tasks, poor judgment.
    - C. Impaired visuospatial abilities.
    - D. Impaired language functions (speaking, reading, writing).
    - E. Changes in personality, behavior.
Probable Alzheimer’s Dementia  

1. Meets criteria for dementia described above and has the following characteristics:
   A. Insidious onset. Symptoms have a gradual onset over months to years, not sudden over hours or days.
   B. Clear cut history of worsening of cognition by report or observation.
   C. The initial and most prominent cognitive deficits are evident on history and examination in one of the following categories:
      a) Amnestic presentation (most common): impairment in learning and recall of recently learned information. Plus evidence of cognitive dysfunction in at least one other cognitive domain.
      b) Non amnestic presentation:
         o Language presentation: the most prominent deficits are in word finding.
         o Visuospatial presentation: the most prominent deficits in spatial cognition like object agnosia, impaired face recognition.
         o Executive dysfunction: the most prominent deficits are impaired reasoning, judgment and problem solving.
   D. The diagnosis of probable AD should not be applied when there is evidence of Stroke or core features of Lewy Body Dementia or prominent features of behavioral variant Frontotemporal dementia, or Primary progressive Aphasia, or evidence of active neurological disease or use of medication that could have a substantial effect on cognition.
Dysfunction in IADLs (Instrumental activities of Daily Living)

- Ability to handle finances
- Ability to handle chores and repairs
- Skills in driving a car / Taking transportation
- Responsibility to medication
- Laundry
- Housekeeping
- Food preparation
- Shopping
- Use of phone
Dysfunction ADLs (Activities of Daily Living)

- Personal hygiene and grooming
- Dressing and undressing
- Self Feeding
- Functional transfers (getting in and out of bed/wheelchair)
- Bowel and bladder management
- Ambulation
Medicare Annual Wellness Visit
Algorithm for Assessment of Cognition

A. Review HRA (especially reports of functional deficits), clinician observations, and self-reported concerns; and query patient and, if available, informant.

Yes

Signs/symptoms of cognitive impairment present

No

Informant available to confirm

B. Conduct brief structured assessment
   - Patient Assessment: GPCOG or Mini-Cog or MIS
   - Informant assessment of patient: AD8 or GPCOG or Short IQCODE

Brief assessment(s) triggers concerns:
   - Patient: GPCOG <3 (5-8 score is indeterminate without informant) or Mini-Cog <3 or MISc4
   - Informant: AD8 ≥2 or GPCOG informant score ≥3 with patient score <8 or Short IQCODE ≥3.38

Yes

Follow-up during subsequent AWV

No

C. Refer for full dementia evaluation or Conduct full dementia evaluation

If informant is available during AWV can follow up same day as AWV and bill for E/M service with CPT codes 99201-99215. If not, schedule new visit for evaluation and request presence of family/companion to facilitate assessment.

* No one tool is recognized as the best brief assessment to determine if a full dementia evaluation is needed. Alternate tools (e.g., MMSE, SLUMS, or MoCA) can be used at the discretion of the clinician. Some providers use multiple brief tools prior to referral or initiation of a full dementia evaluation.

AWV = Annual Wellness Visit; GPCOG = General Practitioner Assessment of Cognition; HRA = Health Risk Assessment; MIS = Memory Impairment Screen; MMSE = Mini Mental Status Exam; MoCA = Montreal Cognitive Assessment; SLUMS = St. Louis University Mental Status Exam; Short IQCODE = short Informant Questionnaire on Cognitive Decline in the Elderly