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Dementia

MHD Clinical Correlation – Neuroscience Block

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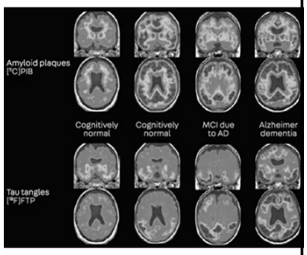
Healthy brain aging

- ***Occasional naming or word finding problems***
- ***Benign retrieval impairments***
- ***Takes longer, but not impaired learning***
- ***Reaction time decreased***
- ***Psychomotor functioning is impaired***
- ***Preservation of global functioning and ADLs.***



Continuum 2019;25:14–33

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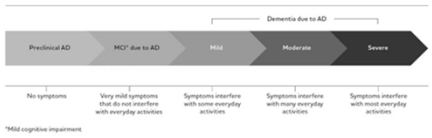
Demographics of Dementia

- ***Alzheimer disease + vascular dementia - 90%***
- ***Demographics of AD***
  - *AD most common cause of dementia > 65 yrs. of age*
  - *5th leading cause of death?*
  - *5% at age 65 yrs.; 35% by 85 yrs.*
  - Currently – 5.8 million; by 2050 it will be 13.8 million in the U.S.
  - *Reduces life expectancy by one-half.*



https://www.alz.org/media/Documents/alzheimers-facts-and-figures.pdf

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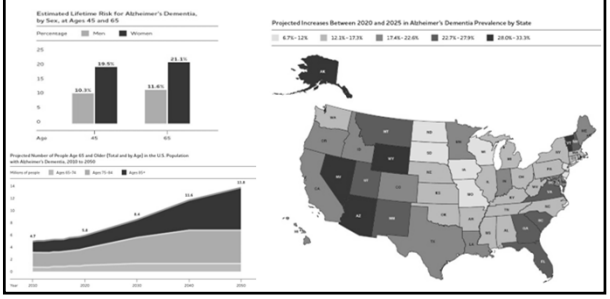
Prevalence change in AD from 2020 to 2025



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Mild Cognitive Impairment (MCI)

- **Demographics**
  - Prevalence of ~ 15-20% > 65yrs
  - *Risk state for dementia*
- **Diagnostic Categories**
  - Amnestic MCI
  - Non-amnestic MCI (executive, visuospatial, language)
- **Diagnosis**
  - *Mild impairment of activities of daily living: self reported or informant, impaired cognitive tests*
  - *Relevance of subjective cognitive concerns ("worried well")*
  - Standard neuropsychological tests
    - ➢ *Montreal Cognitive Assessment (MoCA)* – more useful
    - *Mini-Mental State Examination* (MMSE) - usually normal
  - *Systematic screening (and treatment) – not recommended.*

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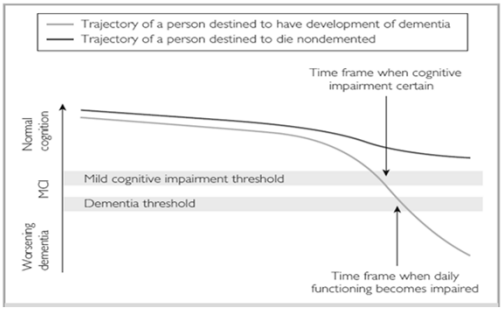

Mayo Clin Proc 2014;89:1452-1459

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Criteria for Dementia

- **Interferes with work or activities**
- **Decline in previous level of functioning**
- **Not explained by delirium or psychiatric disorder**
- **Cognitive impairment is detected**
  - *History from patient or informant*
  - *Objective cognitive assessment*
- **Cognitive/behavior impairment (at least 2)**
  - *Impaired acquisition/remembering new information*
  - *Impaired visuospatial abilities*
  - *Impaired language functions*
  - *Change in behavior/personality*
  - *Impaired reasoning, poor judgment.*

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Risk Factors for Alzheimer Disease

- **Age**
  - 3% age 65-74, 17% age 75-84, 32% age 85 or older
- **Family History**
  - First degree relative – higher risk
- **Genetic mutation (1% of all AD cases)**
  - Amyloid precursor protein (APP) – Chromosome 21
  - Presenilin 1
  - Presenilin 2
- **Down Syndrome (Trisomy 21)**
- **Apolipoprotein E (ApoE) - e4 allele (increased risk)**
  - One allele – 3-fold increased risk
  - Two alleles – 8-12-fold increased risk
  - Incidence of e3 is greatest in the U.S.

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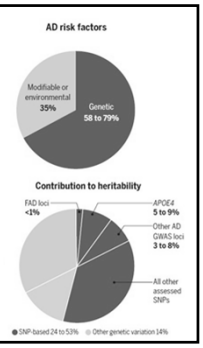
AD Risk factors

Percentage of Blacks/African Americans and European Americans with Specified APOE Pairs

APOE Pair	Blacks/African Americans*	European Americans
e3/e3	45.2	63.4
e3/e4	28.6	21.4
e3/e2	15.1	10.2
e2/e4	5.7	2.4
e4/e4	4.5	2.4
e2/e2	0.7	0.2



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Alzheimer Disease - Diagnosis

- ***Clinical Criteria:***
  - **"Essential" - impairment in learning new information**
  - ***Functional evaluations:***
    - *Mini-Mental State Examination (MMSE)* or Montreal Cognitive Assessment (MoCA)
  - ***Laboratory Testing:***
    - **ROUTINE: CBC,** Chemistry profile, Thyroid functions, Serum B_{12} level
    - **NOT ROUTINE:** Screening for syphilis, ApoE genotyping for AD, Lumbar puncture
  - ***Radiological and other Investigations:***
    - **ROUTINE:** CT or MRI of the brain
    - **NOT ROUTINE:** Volumetric MRI or CT, SPECT scan, PET scan, EEG.

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Psychological Assessment Resources (PAR).

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Appropriate use of Amyloid PET

- **Young onset dementia (< 65 yrs. of age)**
- **AD is possible diagnosis, but uncertain (Increase diagnostic certainly & alter management)**
- **Persistent or progressive unexplained MCI**

Not Indicated

- Already fulfill core criteria for AD and are typical age
- Determine dementia severity
- In asymptomatic individuals or in lieu of genotyping
- Non-medical use (insurance, disability, etc).

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Biomarkers for AD Diagnosis

Biomarkers of Amyloid, Tau, and Neurodegeneration Proposed in the National Institute of Aging-Alzheimer's Association Research Framework for Alzheimer Disease[a]

Amyloid: Aggregated Amyloid-β (Aβ) or Associated Pathologic State
- CSF $A\beta_{1-42}$ or $A\beta_{1-42}$ to $A\beta_{1-40}$ ratio
- Amyloid PET

Tau: Aggregated Tau (Neurofibrillary Tangles) or Associated Pathologic State
- CSF phosphorylated tau
- Tau PET

Neurodegeneration: Neurodegeneration or Neuronal Injury
- Anatomic MRI
- FDG-PET
- CSF total tau

CSF = cerebrospinal fluid; FDG-PET = fludeoxyglucose positron emission tomography; MRI = magnetic resonance imaging; PET = positron emission tomography.
[a] Modified with permission from Jack CR, et al, Alzheimers Dement.[35] © 2018 The Authors.

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Vascular Cognitive Impairment

- **Clinical Criteria**
  - Memory impairment is not required
  - **Classification – Subtypes**
    - Multi-infarct dementia (cortical vascular dementia)
    - Small vessel dementia (subcortical vascular dementia)
    - Strategic infarct dementia
    - Ischemic-hypoperfusion dementia, hemorrhagic dementia, hereditary vascular dementia (CADASIL), AD with cardiovascular disease
  - **Classification – Functional**
    - *No cognitive profile*, but executive function deficit, worse than memory
    - *AD can't be ruled out*, but less likely if <65 yrs. of age
- **Treatment**
  - Address stroke risk factors
  - Anticholinesterase or NMDA inhibitors?.

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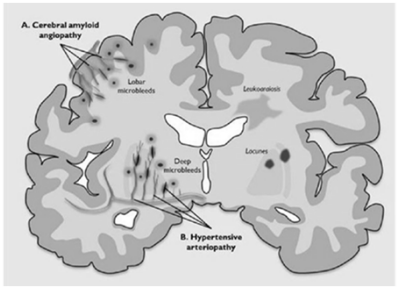
VCI due to small vessel disease



Neurol Clin 35 (2017):231-262

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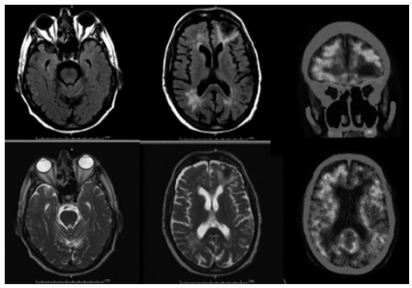
Mixed AD and VCI



Neurol Clin 35 (2017):295-323

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Dementia with Lewy Bodies (DLB)

- ***Clinical Criteria***
  - **"Essential" - impairment in learning new information**
  - **Core features**
    - Fluctuating cognition, attention and alertness
    - Recurrent visual hallucinations
    - REM sleep behavior disorder
    - Spontaneous features of parkinsonism
  - **Supportive Clinical Features**
    - Severe sensitivity to antipsychotic agents, …
  - **Indicative Biomarkers**
- ***Treatment***
  - **Cognition -** *rivastigmine*
  - **REM sleep disorder –** melatonin or clonazepam
  - **Motor Symptoms -** levodopa/carbidopa
  - **Behavioral Symptoms** – Pimavanserin, Quetiapine (BLACK BOX WARNINGS)

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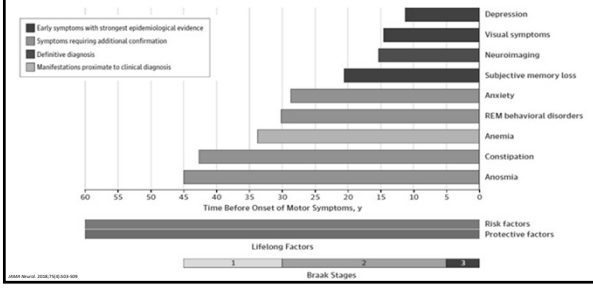
Premotor Symptoms Preceding the Clinical Diagnosis



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Frontotemporal Dementia (FTD)

- ***FTD -*** *heterogeneous with distinct clinical phenotypes, but multiple neuropathological substrates*

✓ ***Behavioral variant*** (>50% of FTD cases)
- Early apathy/inertia
- Socially inappropriate behavior
- Compulsive/ritualistic behavior
- Hyperorality/dietary changes
- Early loss of sympathy/empathy
  - ❖ Neuropsychiatric testing – Executive dysfunction > memory or visuospatial
  - ❖ Neuroimaging

✓ ***Primary progressive aphasias*** (majority of remainder)

✓ *Progressive supranuclear palsy* (PSP), *Corticobasal syndrome* (CBS), Argyrophilic grain disease (AGD).

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Treatment Strategies for AD

- ***Establish an early/accurate diagnosis of AD***

➢***Treating medical comorbidities***
- *(Diabetes, HTN, Depression, Smoking, Obesity, physical inactivity, educational inactivity)*

➢***Ensuring that appropriate services are provided***

➢***Addressing long-term well-being of caregivers***

- ***Early institution of targeted drugs***
- ***Treating behavioral & psychological symptoms.***

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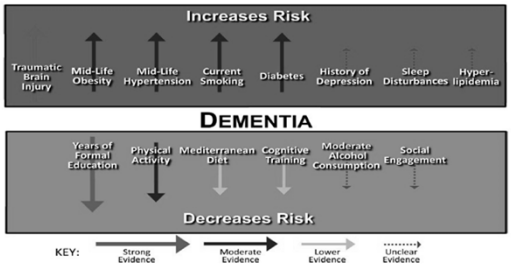
Modifiable risk factors for dementia



Alzheimer & Dementia 2015;11:718-726

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AD Cognitive Treatment

- ***Mild*** ***(Impaired mental ability and mood swings)***
  - **Rivastigmine, Donepezil, Galantamine**
    - Switch to another, if ineffective
- ***Moderate*** ***(Behavioral disturbances are frequent)***
  - **Rivastigmine, Donepezil, Galantamine**
    - Switch to another, if ineffective or add Memantine
- ***Severe*** ***(Physical problems are dominant)***
  - **Memantine added**

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Behavioral and psychological symptoms

Need to perform a Neuropsychological "Checklist"

- ✓ **Behavioral dysfunction (agitation, aggressiveness, irritability, disinhibition, aberrant motor)**
- ✓ **Psychosis (delusions, hallucinations)**
- ✓ **Mood disturbance (depression, anxiety, elation, apathy)**
- ✓ **Night-time behavior**
- ✓ **Appetite and eating disturbance.**

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Treatment of behavioral and psychological symptoms

- ***Non-pharmacological***
- **Pharmacological**
  - ***General tenets***
    - Identify and target symptoms (one at a time)
    - Quantify adverse behaviors
    - Remove other causes
    - ***Sequential, rationale and limited monotherapy***
  - ***Depression and Anxiety***
  - ***Agitation → black box warnings***
  - ***Psychosis → black box warnings.***

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Pharmacological treatment for non-cognitive symptoms

- ***Depression or Anxiety***
  - *Citalopram (Celexa™)*
  - *Sertraline (Zoloft™)*
  - *Venlafaxine (Effexor™)*
  - *Trazodone (Desyrel™)*
- **Psychosis**
  - *Quetiapine (Seroquel™)*
  - *Risperidone (Risperdal™)*
  - *Pimavanserin (Nuplazid™)**

Antipsychotics are not indicated for the treatment of dementia-related psychosis.

In April 2005, FDA notified healthcare professionals that patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death and also associated with conventional antipsychotics.

** Treat hallucinations/delusions in people with Parkinson disease*

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