



Screen, Gene, and Intervene:
The Diagnostics, Genetics, and Pharmacologics of Dementia

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Speech and Language Pathology
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Outline 


- Diagnostic work-up and general management of dementia
- Genetics of dementia, focusing on:
 - Alzheimer's disease
 - Frontotemporal lobar degeneration (FTD)
- Pharmacologic management of dementia
- Q&A

Learning Objectives 


1. Compare the diagnosis and management of dementia from the PCP/geriatrics, psychiatry, and neurology
2. Describe utility of genetic testing, including APOE genotyping
3. Assess utility of available pharmacologic management of dementia, with a focus on monoclonal antibodies in Alzheimer's disease


Disclosure 

- Principal investigator/study physician for ongoing and previously conducted Alzheimer’s disease clinical trials at Vanderbilt, with industry sponsors including:
 - AbbVie
 - Acadia
 - Genenetch/Roche
 - Janssen
 - CND


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What words come to mind when you think of dementia? 

When poll is active respond at [PollEv.com /lacosta552](https://poll.ev.com/lacosta552) Send **lacosta552** to **37607** 


Mild Cognitive Impairment
(Minor neurocognitive disorder)



1. Concern regarding a change in cognition
2. Impairment in ≥ 1 cognitive domain
 - Memory, executive function, attention, language, visuospatial skills
3. Preservation of independence in functional abilities
4. Not demented

Albert et al., *Alzheimer's and Dementia* (2011)


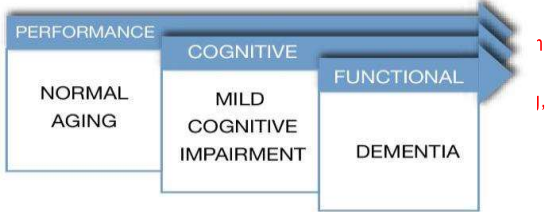
Dementia (Major neurocognitive disorder)



1. Impairment in short- and long-term memory associated with
 - a. impairment in abstract thinking,
 - b. impaired judgment,
 - c. other disturbances of higher cortical function,
 - d. or personality change.
2. Disturbance severe enough to interfere significantly with work, usual social activities, or interpersonal relationships
3. Not delirious

DSM-IV

MCI vs. Dementia

3. Preservation of independence in functional abilities
4. Not demented
2. Disturbance severe enough to interfere significantly with work, usual social activities, or interpersonal relationships
3. Not delirious

Diagnosing Dementia



- Who diagnoses dementia?
 - PCP usually the first to hear about this
 - May be referred:
 - Geriatrics
 - Psychiatry
 - Neurology
- What is necessary for the diagnosis of dementia?
 - Clinical history
 - Cognitive assessment

Diagnostic Evaluation of Cognitive Impairment



- Laboratory serologies
 - E.g., CMP, CBC, TSH/T4, vitamin B12
- Brain imaging
 - CT head
 - MRI brain
- Referral?
 - Specialty
 - PT
 - OT
 - SLP

Dementia

Alzheimer's and Dementia banner

Alzheimer's Disease
Vascular Dementia
Alcohol Related Dementia

Mixed Dementia
Lewy Body Disease
Frontotemporal Dementia

<http://www.alzsd.org/resources/>


Types of dementia

- Alzheimer's disease
- Frontotemporal lobar degeneration
- Dementia with Lewy bodies
- Vascular dementia
- Normal pressure hydrocephalus
- Progressive Supranuclear Palsy
- Corticobasal Syndrome
- Parkinson's disease dementia
- ... and many, many more!


Primary progressive aphasia

- Neurodegenerative diseases characterized by early and prominent language impairment occurring in the relative absence of cognitive impairment, behavioral disturbance, or motor symptoms.


Alzheimer's Disease



- **Features**
 - often **getting lost/disoriented**
 - prominent **forgetting** and **repeating (amnesic)**
 - Typically **anosognosic**
- **Deposition of amyloid and tau**




PollEverywhere Question




- What variant(s) of primary progressive aphasia (PPA) is/are most often associated with Alzheimer's as the underlying pathology?
- A. Logopenic aphasia
- B. Semantic aphasia
- C. Agrammatic/nonfluent aphasia
- D. Primary progressive apraxia of speech


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Alzheimer's Disease



- **Features**
 - often **getting lost/disoriented**
 - prominent **forgetting** and **repeating (amnesic)**
 - Typically **anosognosic**
- Deposition of amyloid and tau
- PPA variant: **logopenic**
 - Impaired sentence repetition
 - Word-finding difficulty



Logopenic PPA

Symptoms

- Decreased spontaneous language: "few er words"
- Anomia
- Impaired repetition and pseudoword reading
- Comprehension relatively intact

Imaging

- Left hemisphere posterior temporal and inferior parietal lobes

Pathology: Alzheimer's > FTD

Gorno-Tempini et al Neurology (2011)
Kishner Neuropsychiatr Dis Treat (2014)
Migliaccio et al Neurology (2009)

MRI


FDG-PET brain

"Severely decreased FDG uptake in bilateral frontal and temporal lobes with mild to moderate decreased uptake in bilateral parietal lobes. These findings most likely represent frontal temporal dementia but a more intense form of Alzheimer's cannot be excluded."

| FTLD | |
|-----------------------------------|--|
| Frontotemporal lobar degeneration | Neurodegenerative disease process with "focal" symptoms of progressive language dysfunction or behavioral changes |
| Clinical Features | 1. Behavioral variant <i>Personality change/alterations in social conduct (disinhibition)</i> Appetite <i>Abulia/apathy</i> Decline in hygiene <i>Language variants</i> 2. Semantic dementia 3. Progressive non-fluent aphasia |
| Pathology | Tau (Pick bodies) |
| Neurological Exam | Disinhibited behavior or personality change Frontal release signs, hyperreflexia, fasciculations, etc. Bulbar symptoms |
| Diagnostic work-up | Genetic variants |
| Imaging | MRI (fronto-temporal atrophy) or FDG-PET brain (fronto-temporal hypometabolism) |
| Treatment | Supportive; behavioral rx with SSRIs |

FTLD: Diagnosis

- Personality change and alterations in social conduct
 - Disinhibition
 - "witzelsucht"
- Appetite
- Abulia/apathy
- Decline in hygiene
- Anosognosic
- Memory loss usually not prevalent




Kirshner HS (2014). Frontotemporal dementia and primary progressive aphasia: a review. *Neuropsychiatr Dis Treat* 10:1045-55. doi: 10.2147/NDT.S38821.

PollEverywhere Question

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FTLD Language Variants

Non-fluent/Agrammatic PPA


- Effortful, halting speech
 - “Broca-like”
- Simplified, “agrammatic”
- Comprehension relatively preserved
 - word
 - sentence

Semantic PPA

- Fluent aphasia
- Anomia
- Impaired word meaning
- Repetition intact
- Surface dyslexia



“yacht”




“colonel”

Kishner Neuropsychiatr Dis Treat (2014)


FTLD Language Variants

Non-fluent/Agrammatic Aphasia



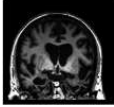
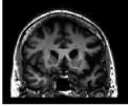

- Peri-Sylvian atrophy

Semantic Aphasia




- Anterior temporal lobe atrophy

UCSF: <http://memory.ucsf.edu/ftld/overview/ftld/forms/multiple/sd>

| | | |
|---|---|--|
| <p style="text-align: center;">FTLD</p> <p>Semantic</p> <ul style="list-style-type: none"> • <u>Fluent</u> aphasia • Anomia • Impaired word meaning • Repetition intact • Surface dyslexia • Radiology: anterior temporal atrophy <p style="text-align: center; font-size: x-small;">svPPA</p>  | <p>Non-Fluent/Agrammatic</p> <ul style="list-style-type: none"> • “Broca-like” • Simplified, “agrammatic” • Comprehension relatively preserved • Radiology: peri-Sylvian atrophy <p style="text-align: center; font-size: x-small;">nvPPA</p>  | <p style="text-align: center; color: purple;">AD</p> <p>Logopenic</p> <ul style="list-style-type: none"> • ↓spontaneous language production (“fewer words”) • Anomia • Impaired repetition • Comprehension relatively intact • Radiology: temporoparietal atrophy <p style="text-align: center; font-size: x-small;">lvPPA</p>  |
|---|---|--|


PPA Clinical Features

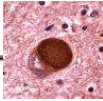


| Characteristic | Non-fluent/ agrammatic | Semantic | Logopenic |
|----------------|---------------------------|-------------------------------------|-------------------------|
| Fluency | Non-fluent | Fluent | Fluent |
| Naming | Some anomia | Some anomia | Anomia |
| Repetition | Non-fluent | Fluent | Impaired |
| Comprehension | Intact for simple items | Impaired, even at single-word level | Intact for simple items |
| Reading | Intact for short items | Surface alexia | Intact for simple items |
| Nonsense words | Normal | Impaired for irregular words | Impaired |

Modified from: Kirshner *Neuropsychiatr Dis Treat* (2014)


Lewy Body Dementia (DLB)






| | |
|-----------------------------------|--|
| DLB | Dementia secondary to Lewy bodies (alpha-synuclein) with fluctuating cognition, hallucinations, and parkinsonism |
| Clinical Features: CORE | Dementia: Attention, dyexecutive, visuospatial, memory loss Fluctuating cognition Visual hallucinations Parkinsonism REM disorder Parkinsonism (>1 cardinal feature) |
| Pathology | Lewy bodies (alpha-synuclein protein) |
| Neurological Exam | Parkinsonism |
| Diagnostic work-up | Sleep study if concern for REM disorder Neuropsychological testing |
| Imaging | CT/MRI nonspecific; FDG-PET brain (occipital hypometabolism) |
| Treatment | AChE inhibitors for memory; dopaminergic therapy for parkinsonism |

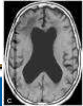

Vascular Dementia






| | |
|--------------------------|--|
| Vascular dementia | NINDS-AIREN criteria <ul style="list-style-type: none"> • Onset or worsening of dementia is w/in 3 months s/p clinical stroke • Imaging shows evidence of bilateral infarcts in cortical regions, basal ganglia, thalamus, or white matter <ul style="list-style-type: none"> • Can also be secondary to accumulation of "silent" infarcts • Focal deficits on neurological exam |
| Clinical Features | " stepwise " decline cognitively, with accompanying focal neurological deficits |
| Pathology | Stroke |
| Neurological Exam | Focal neurological deficits (cognitively, often aphasia) |
| Diagnostic work-up | Arrhythmias, lipids, hemoglobin A1c |
| Imaging | NCHCT (hemorrhagic stroke) MRI brain (acute ischemic stroke: DWI and ADC changes) |
| Treatment | Managing stroke risk factors Symptomatic treatment (e.g., depression) |

Normal Pressure Hydrocephalus (NPH)


| Normal pressure hydrocephalus | Chronic communicating hydrocephalus |
|-------------------------------|--|
| Clinical Features | Mental impairment, gait disturbance, and incontinence "weird, wet, and wobbly" |
| Pathology | n/a |
| Neurological Exam | Cognitive changes, magnetic gait |
| Diagnostic work-up | CT or MRI brain Lumbar puncture (NORMAL opening pressure) with high volume tap (>30 cc) → yields symptomatic improvement CSF typically without abnormalities |
| Imaging | Ventriculomegaly |
| Treatment | Ventriculoperitoneal shunt |

Diagnosing Dementia: inpatient?




- Need to rule out alternative causes
- Can't diagnose when somebody is delirious
 - Outpatient > inpatient


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2. **Describe utility of genetic testing, including APOE genotyping**
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Genetics 

- Most dementias do not have a genetic cause
- A minority of patients with neurodegenerative dementia get referred to genetic counseling


Genetics: Alzheimer's disease 

- Most dementias do not have a genetic cause
- Alzheimer's disease (AD)
 - Early onset AD, <65 yo
 - Presenilin, APP
 - APOE genotype

Genetics: Frontotemporal lobar degeneration 


- Most dementias do not have a genetic cause
- Frontotemporal lobar degeneration
 - C9orf72
 - MAPT
 - Progranulin

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Pharmacologic Therapies



- Major categories of pharmacological interventions for dementia
 - **Cholinesterase inhibitors**
 - **NMDA receptor antagonists**
 - Monoclonal antibodies
 - Antidepressants and anxiolytics
 - Antipsychotics
 - Hypnotics

Pharmacologic Therapies



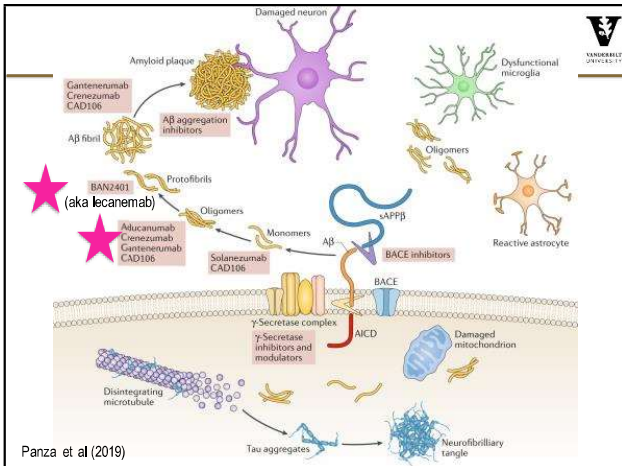
| Drug category | Drug names | AD | FTLD | DLB | PSP/CBS | PDD | VD |
|---------------------------|--|-------------------------------------|--------------------------------|--------------------------------|--------------------------------|--------------------------------|-----------------|
| Cholinesterase inhibitors | Donepezil | ✓ | X | ✓ | X | ✓ | ✓ |
| | Rivastigmine | ✓ | X | ✓ | X | ✓ | ✓ |
| | Galantamine | ✓ | X | ? | X | ✓ | ✓ |
| NMDA r. ant. | Memantine | ✓ | X | ✓ | X | ? | ✓ |
| Antidepressants | SSRIs, SNRIs | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Anxiolytics | Bupropion, SNRIs | ✓, avoid benzodiazepines in general | | | | | |
| Hypnotics, REM disorder | Melatonin | ✓ | ✓ | ✓ | | | |
| | trazodone | ✓ | ✓ | ✓ | | | |
| | Mirtazapine, suvorecant | ✓ | ✓ | ✓ | | | |
| | Clonazepam | X | X | ✓ | | | |
| Antipsychotics | Primarsanserin, Clozapine, Clozapine risperidone | ✓, with caution | Risperidone o/w ?/✓ | Risperidone o/w ?/✓ | Risperidone o/w ?/✓ | Risperidone o/w ?/✓ | ✓, with caution |
| Parkinsonism | Carbidopa/levodopa Dopamine agonists Amantadine | | | ✓ X ? | ✓ X ✓ | ✓ X ✓ | |
| Dystonia | Baclofen | | | | ✓ | | |
| | Clonazepam | | | | ✓ | | |
| | Benzhexolol Botulinum toxin | | | | ✓ X ✓ | | |

Dementia Treatment



- Drugs used depend on the disease: cannot be used across all dementias
- E.g., cholinesterase inhibitors can make behaviors worse in FTLD
- E.g., certain antipsychotics can make symptoms of dementia with Lewy bodies worse

Fekiman et al. *Lancet Neurol* (2007)
 Lu et al *Neurology* (2009)
 McShane et al *Cochrane Rev* (2006)
 Salloway et al *Neurology* (2004)



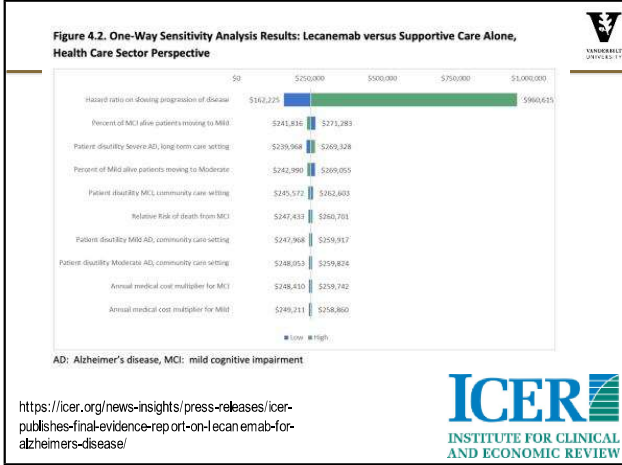
Panza et al (2019)

Table 3.4. Adverse Events

| Harms | 12/15 | 15/15 |
|---|-----------------|-----------------|
| Any Adverse Event, n/N (%) | 126/898 (14.0%) | 101/897 (11.3%) |
| Serious Adverse Event, n/N (%) | 62/898 (6.9%)* | 26/897 (2.9%)* |
| Discontinuation Due to Adverse Event, n/N (%) | 155/898 (17.3%) | 81/897 (9.0%) |
| Any ARIA-E, n/N (%) | 113/898 (12.6%) | 15/897 (1.7%) |
| Symptomatic ARIA-E, n/N (%) | 25/898 (2.8%) | 0/897 (0%) |

ARIA-E: amyloid-related imaging abnormalities
 n: number of participants
 AE, lost to follow-up, subject other.

<https://icer.org/news-insights/press-releases/icer-publishes-final-evidence-report-on-lecanemab-for-alzheimers-disease/>




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References for PPA




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Thank you for your attention!




Questions?

healthy brain



advanced alzheimer's



https://www.alz.org/brainour/healthy_vs_alzheimers.asp
