Duke Dementia Family Support Program

Caregiver Connections

An Educational Webinar Series with the Experts

The presentation will begin shortly.

dukefamilysupport.org
919-660-7510

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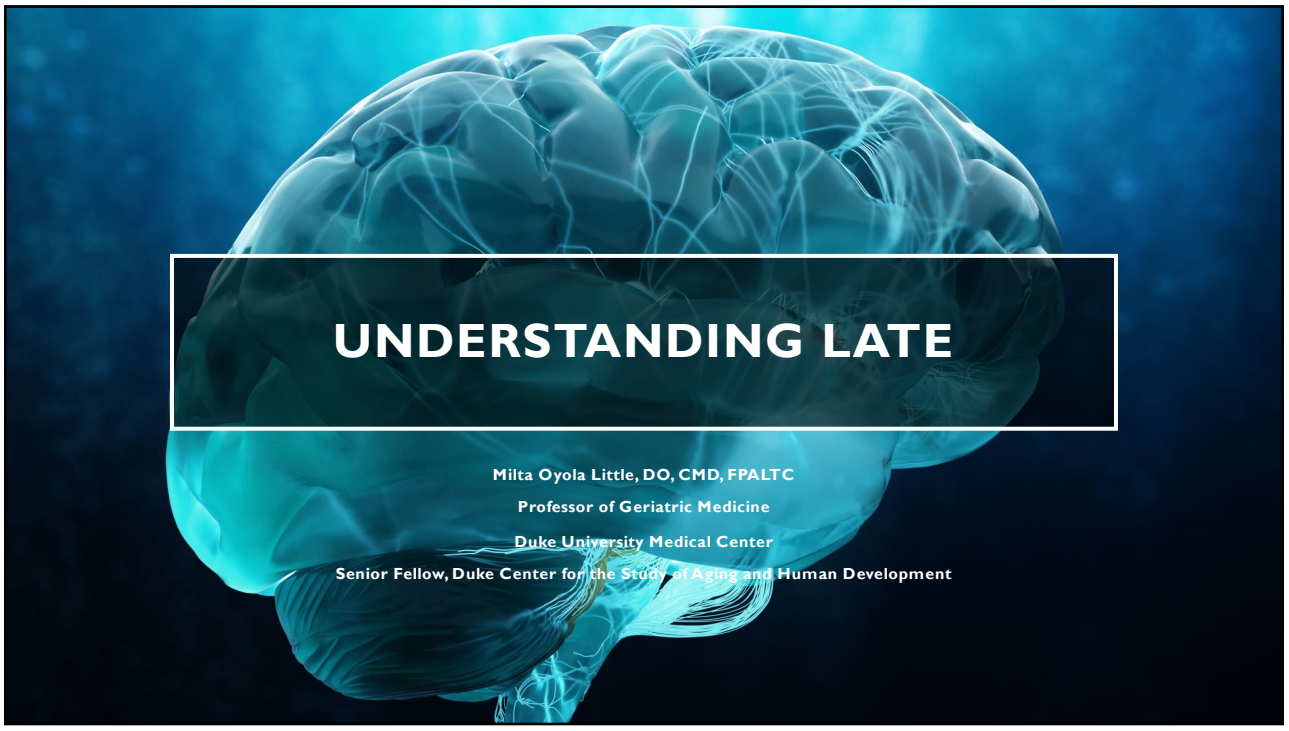

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OBJECTIVES

- Define LATE – Limbic-predominant Age-related TDP-43 Encephalopathy
- Distinguish LATE from Alzheimer's disease and other forms of dementia
- Discuss the current approach to management of LATE.

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DEFINITIONS

- **Neurodegeneration** = the slow, progressive loss of structure or function of neurons; brain cells are breaking down, fading away, or dying over time.
- **Pathy** = disease, damage, abnormal
- **Proteinopathy** = diseased, damaged, and/or abnormal proteins that are naturally occurring and necessary to the brain and body
- **Amnestic brain change** = trouble forming new memories or recalling recent events due to neurodegeneration; prominent, early memory loss is the defining trait; typical of Alzheimer's Disease

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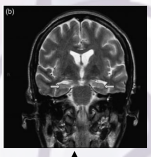
ALZHEIMER'S IS WELL KNOWN

Alzheimer's disease is an amyloid protein mediated tau proteinopathy

Amyloid β build-up → **Tau build-up** → **CaTAUstrophe neurodegeneration** → **Dementia**



- Trisomy 21 (Down Syndrome)
- Familial AD (APP, PSEN1, PSEN2)
- APOE-ε4

Spread of tau tangles into the neocortex, i.e., "CaTAUstrophe"

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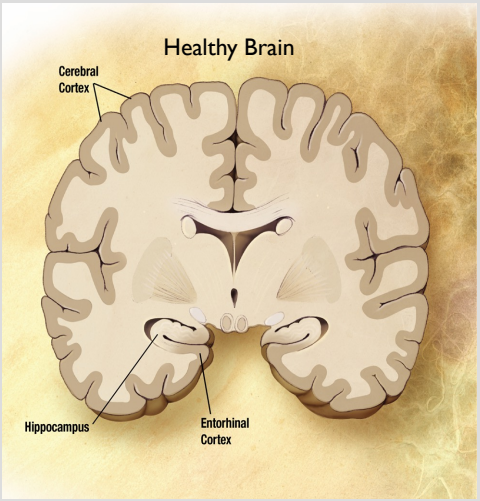
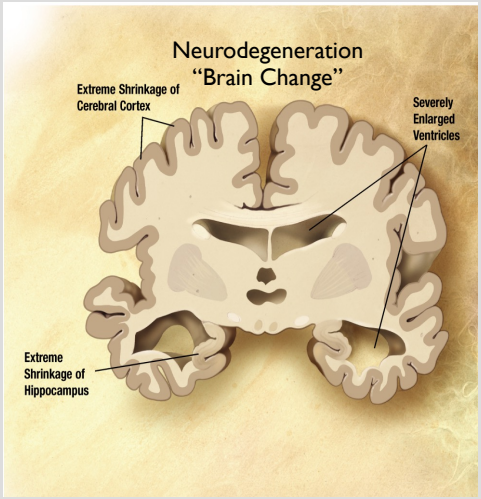
WHAT NEURODEGENERATION LOOKS LIKE ON MRI IMAGING





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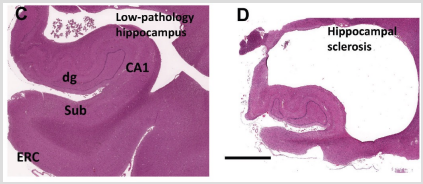
HISTORY OF LATE



1994
Hippocampal Sclerosis of Aging (HS-A)

2007
HS-A associated with TDP-43 Proteinopathy

2024
Clinical criteria for LATE first published

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Phosphorylataed TDP-43 (abnormal protein) found in Frontotemporal and ALS brains

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LATE pathology first described in literature

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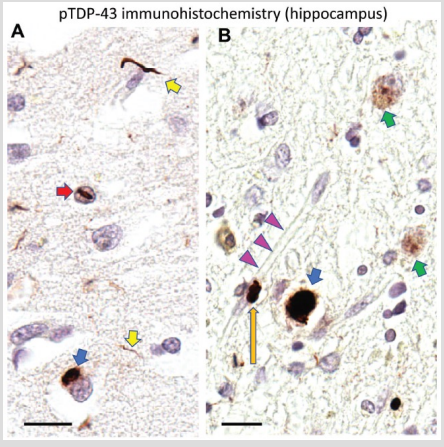
WHAT IS LATE?



Mislocalized, misfolded TDP-43 protein in the brain, analogous to Tau

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WHEN I SUSPECT LATE

TABLE 1 LATE as the primary diagnosis.

I. Core clinical syndrome[a] (1 and 2 required)

1. Primary amnestic syndrome with temporo-limbic memory loss.
2. Other cognitive domains largely spared until much later in the course.
3. May have mild semantic memory impairment.
4. Indolent course with predominant amnestic syndrome present for at least 2 years.
5. Age generally >75 years old.

II. Required imaging

Significant hippocampal atrophy (out of proportion to global atrophy)

III. Required supportive features for probable LATE

A negative test of one of the following to rule out amyloid beta (Aβ):

a. Amyloid PET
b. CSF $A\beta_{42/40}$
c. CSF p-tau_{181}/$A\beta_{42}$ or t-tau/$A\beta_{42}$

TDP-43 biomarkers do not yet exist.

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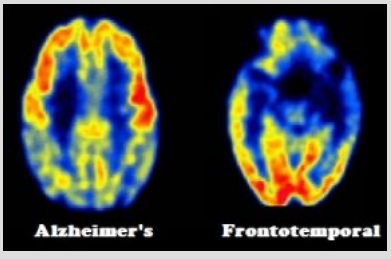
FRONTOTEMPORAL DEMENTIA (FTD)

- FTD is also a TDP-43 proteinopathy but is clinically distinguishable from LATE
- Results from **progressive degeneration** of **frontal and temporal lobes**
- **Affects personality**, causing a **decline in social skills** and inability to understand/read another's emotions
- Can affect **language** and **motor skills**
- Behavior and personality changes manifest long before memory loss
- Occurs at a **younger age** and is more common than Alzheimer's in people <60



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LATE: THE PRIMARY ALZHEIMER'S MIMIC

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~ 1 in 3 people over age 85 have LATE brain changes at autopsy

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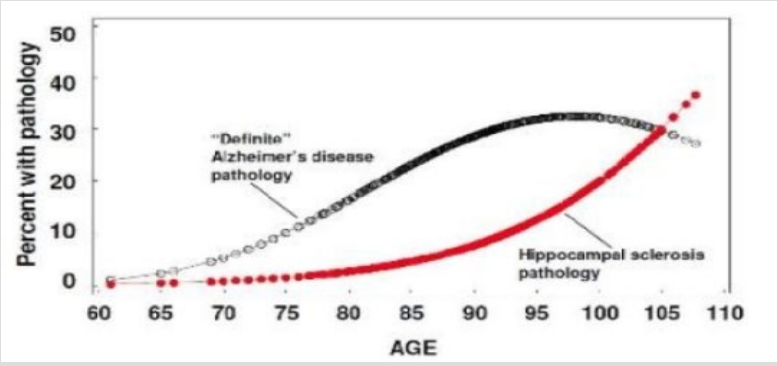
LATE OCCURS LATER IN LIFE



Nelson PT1, et al. Brain. 2011 May;134(Pt 5):1506-18.

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ALZHEIMER AND LATE PATHOLOGY FREQUENTLY CO-EXIST

- ~50% of severe Alzheimer Disease pathology have coexisting LATE pathology
- APOE 4 appears to be a risk factor for both; other genetic links are emerging
- "**Polyproteinopathy**" with abnormal amyloid, tau, TDP-43 and alpha-synuclein (Lewy Body Disease) is a cause of rapidly progressing and severe dementia, often with psychotic symptoms.

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HOW IS LATE MANAGED?

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MAIN NON-DRUG INTERVENTIONS FOR DEMENTIA

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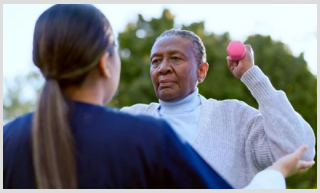
EXERCISE – IT'S NEVER TOO LATE!



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EXERCISE AND DEMENTIA

- **Exercise has been shown to improve quality of life for all stages of Dementia and Alzheimer's**
- It likely **works better than our best medications** in improving symptoms and behavioral issues
  - Can reduce risk of stroke and improve high blood pressure, diabetes, and cholesterol, all of which are risk factors for vascular dementia
  - Improved physical fitness can allow for longer independence
  - Reduces risk of falls
  - Improves mood
  - Improves sleep

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OCCUPATIONAL THERAPY

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MIND DIET

Mediterranean-DASH Intervention for Neurodegenerative Delay = MIND

Foods to Encourage	Food to Avoid/Limit
1-2 Servings of Fatty Fish	Butter and Margarine
Green leafy vegetables	Cheese
Nuts	Red Meat
Olive Oil	Fried Food
Whole Grains	Pastries and Sweets
Beans	
Poultry	
Non-starchy vegetables (fresh or frozen)	

https://www.healthline.com/nutrition/mind-diet

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MANAGEMENT: NON-PHARMACOLOGIC

- Optimize medical comorbidities – diabetes, heart disease
- Screen for hearing loss
- Screen for depression and anxiety
- Plan for next steps: Advance Directives

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MANAGEMENT: NON-PHARMACOLOGIC

Early on: **Prioritize safety**

- Driving
- Weapons in home
- Access to adequate nutrition (MIND diet)
- Medication management
- Finances

Further information about driving safety and planning
https://www.thehartford.com/resources/mature-market-excellence/driving-safety
Driving retirement planning: https://planfortheroadahead.com/aging-driving/sensory-physical-changes/

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MEDICATIONS FOR LATE?

- There are **no proven cures or disease-slowing treatments…yet**
- Goal is to **maximize cognitive abilities** for as long as possible (improve symptoms)
- There are **4 FDA approved oral medications** to treat dementia symptoms:
  - Donepezil (Aricept)
  - Rivastigmine (Exelon)
  - Galantamine (Razadyne)
  - Memantine (Namenda)

Table 5
Summary of Drugs to Improve Cognitive Function

Generic Name	Brand Name	Dosage Forms	Mechanism	Starting Dosage	Goal Dosage
Donepezil	Aricept	IR tablet ODT	Cholinesterase inhibitor	5 mg/day	10 mg/day
Galantamine	Razadyne	IR tablet ER tablet	Cholinesterase inhibitor	4 mg bid or 8-12 mg/day	8 mg/day (ER) 16-24 mg/day (ER)
Memantine	Namenda	IR tablet	NMDA inhibitor	5 mg/day	10 mg bid
Rivastigmine	Exelon	Patch IR capsules Oral solution	Cholinesterase inhibitor	4.6 mg per 24 h 1.5 mg bid	9.5 mg per 24 h 6 mg bid

IR: immediate release; ODT: orally disintegrating tablet; ER: extended release; NMDA: N-methyl-D-aspartate (glutamate).

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Is the person taking the medication for one of the following reasons:

ChEIs (donepezil, rivastigmine or galantamine):

- Alzheimer's disease, dementia of Parkinson's disease, Lewy body dementia or vascular dementia.

Memantine:

- Alzheimer's disease, dementia of Parkinson's disease or Lewy body dementia.

Donepezil: 5mg, 10 mg

Rivastigmine capsules: 1.5 mg, 3 mg, 4.5 mg, 6 mg

Rivastigmine patch (24h): 4.6 mg, 9.5mg , 13.3mg

Galantamine CR capsule: 8mg, 16mg, 24 mg

Memantine: 10 mg, 20 mg

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COMMONLY USED MEDICATIONS THAT SHOULD BE AVOIDED IN PEOPLE WITH OR AT RISK OF MEMORY LOSS

https://www.drugs.com/article/anticholinergic-drugs-elderly.html

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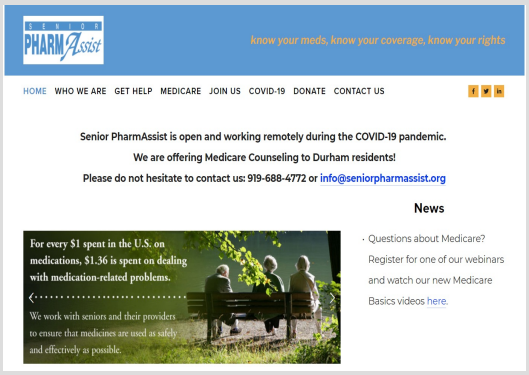
MEDICATIONS



www.seniorpharmassist.org/

- Bring all your medications to your appointments and keep an updated list available
- Create a system for keeping track of your medications

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FUTURE OF LATE

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Hippocampal Sclerosis of Aging (HS-A)

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THE FUTURE

TDP-43 biomarkers (imaging, CSF, blood)
Genetic links
Disease-modifying treatments

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PROMOTE AND ENGAGE IN INTERGENERATIONAL PLAY!!

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Thank you for joining us today!

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