Overview of Mild Cognitive Impairment and Dementia for an Interprofessional Team

MODULE 1

LAKE ERIE INTEGRATED GERIATRIC HEALTH TEAM

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Outline

- Normal aging versus dementia
- Mild cognitive impairment
- Types of dementia: Alzheimer's disease and related dementias (ADRD)
  - Alzheimer's disease
  - Vascular dementia
  - Lewy body dementia
  - Frontotemporal degeneration
  - Other rare causes of dementia

Learning Objectives

After reviewing this module, the learner will be able to:

- Identify differences between the cognitive, functional, and behavioral changes of normal aging and those associated with mild cognitive impairment and dementia.
- List the most common types of dementia.
- Identify the prevalence, risk factors, signs and symptoms, and rate of progression of dementia.
- Identify the stages of dementia.

Key Take-Home Messages

- Most forms of dementia come on slowly and may be preceded by mild cognitive impairment (MCI). MCI does not include functional losses.
- Alzheimer's disease is the most common but not the only type of dementia.
- Diagnosis of dementia requires impairment in two or more core cognitive functions
- Dementia of Alzheimer's disease has been described as progressing through three stages: early, middle, and late stage.
- Diagnosis is predominantly made by primary care provider (PCP), geriatrician, neuropsychologist, or neurologist.
- Not all memory issues are indicative of Alzheimer's disease or another type of dementia.

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Normal Aging Versus Dementia: Identifying the Differences

Suspicion and recognition of dementia versus normal aging are based on changes that occur across the following capabilities:

- Cognitive function
  - Memory
  - Executive function
  - Information processing
- Visuospatial function
- Other sensory changes
- Language skills
- Ability to perform basic and instrumental activities of daily living (ADLs and IADLs, respectively)
- Appearance of specific behavioral and psychologic symptoms

Cognitive Function

- Cognitive function refers to how a person becomes aware of, perceives, or comprehends ideas (Anstey et al., 2004).
- It declines gradually while young and more rapidly among older adults (>60s) (Anstey et al., 2004).
- Many other medical and psychological factors can influence cognitive function (Pankratz et al., 2015; Mayo Clinic, 2017b; UCSF Memory and Aging Center, 2017; Heaton et al., 2010; Karakis et al., 2016; Emory Alzheimer's Disease Research Center, 2017; HelpGuide.org, n.d.; Pagoria et al., 2011).

Executive Function

- Executive function refers to a set of mental or cognitive skills believed to be controlled by the frontal lobe, anterior cingulate, prefrontal cortex, basal ganglia, and thalamus (UCSF Memory and Aging Center, 2016b; Rosenbloom et al., 2012).
- There are 2 main types of executive functions (USCF Memory and Aging Center, 2018c):
  - Organization: attention, managing time, planning and organizing, remembering details, sequencing, and working memory
  - Regulation: self-control, emotional regulation, decision-making, and moral reasoning
- Impairments in executive function can lead to difficulty planning, emotional swings and changes, loss of fine motor skills, apathy, and socially inappropriate behaviors (USCF Memory and Aging Center, 2018c).

Memory Loss

- Many different types of memory (Arlt, 2013; Atkinson & Shiffrin, 1968)
- General types of memory (Arlt, 2013; UCSF Memory and Aging Center, 2018d):
  - Short-term (or working) memory (<1 min)
  - Long-term (lifetime) memory
    - Sensory memory: Visual (iconic), auditory (echoic), smell-based (olfactory), taste-based, or haptic (touch-based) memory

Functional Abilities: ADL

- Activities of daily living (ADL) refer to functional self-care activities we perform every day.
- ADLs are separated into basic ADL and instrumental ADL (IADL) (Galvin, 2012; Gold, 2012).
  - Basic ADL: Bathing, eating, dressing, grooming, toileting, and transferring
  - IADL: More complex activities such as using a telephone, shopping, preparing meals, doing housework, and attending to finances. Successful completion of IADL requires intact executive function.

Normal Aging Versus MCI Versus Dementia

- It is important to distinguish between normal aging, mild cognitive impairment, and a neurodegenerative disorder (dementia) (Wakefield et al., 2014) in order to initiate appropriate and early care.
- In normal aging, the body and brain gradually slow down, but intelligence remains stable (Dumas, 2015).
- Persons who have MCI have notable problems with memory or other core brain functions, but impairments are not sufficient to interfere with daily life (Arevalo-Rodriguez et al., 2016; Brown, et al., 2011; Stewart, 2012).
- Dementia encompasses a range of neurodegenerative brain disorders; persons living with dementia (PLwD) have severe enough mental decline so as to interfere with daily life.
- Many factors are considered in a differential diagnosis between natural aging, MCI, and dementia (Anstey et al., 2004; Emory Alzheimer's Disease Research Center, 2017; UCSF Memory and Aging Center, 2018d).

Normal Aging

- Normal aging is characterized by (Dumas, 2015; Emory Alzheimer's Disease Research Center, 2017; UCSF Memory and Aging Center, 2018d):
  - A general slowing of cognitive performance
  - A decrease in mental flexibility
  - Some difficulties finding the right word (Wakefield et al., 2014)
  - A mild decrease in short-term (working) memory (Wilson et al., 2011)
  - Intact memory for current events
  - Independence in ADL and IADL
  - Retention of verbal abilities and vocabulary
- Changes in perceptual systems or speed of processing associated with normal aging can influence cognitive processes such as attention and memory (Dumas, 2015).

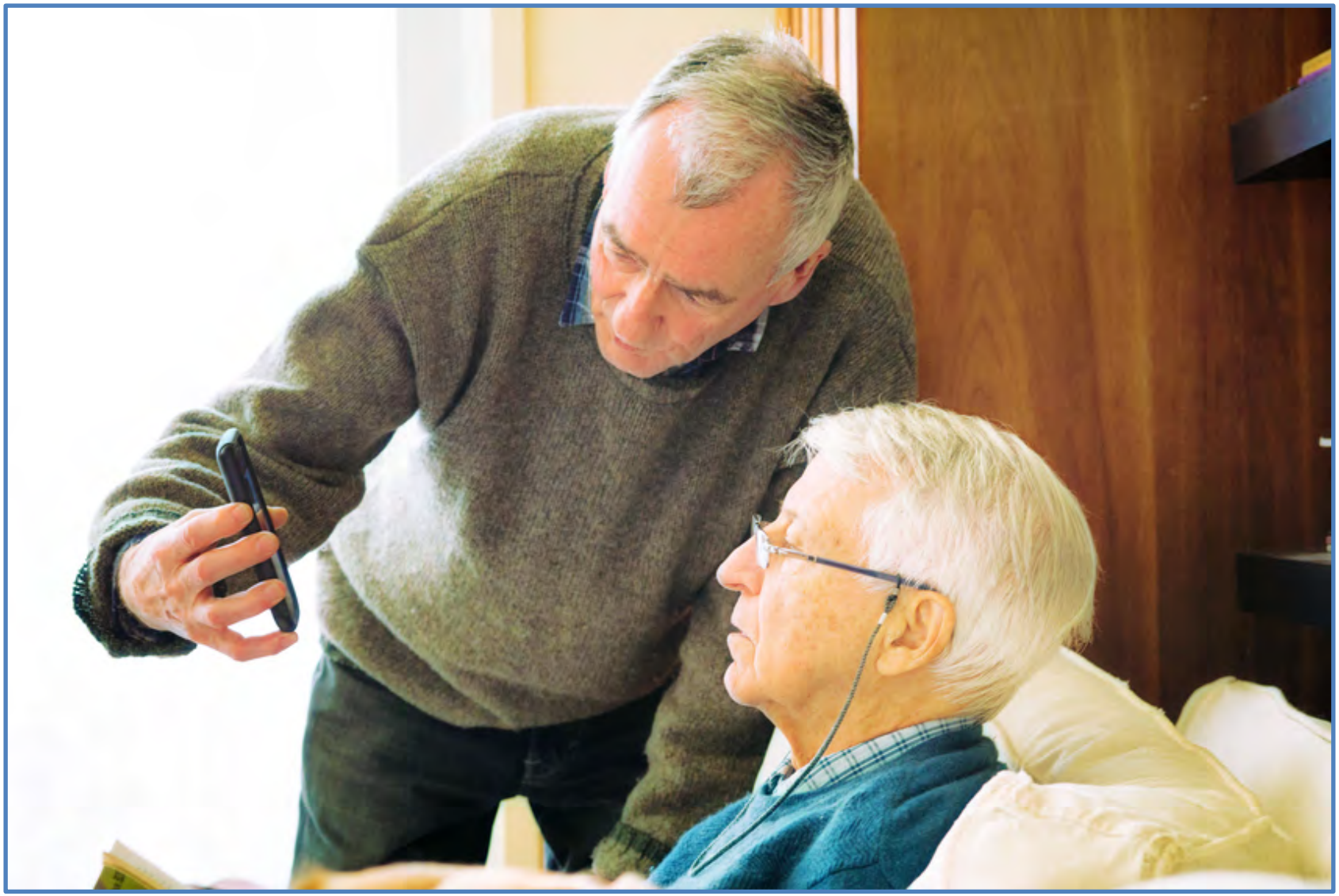
Normal Aging, continued

- As people age, they retain their ability to perform basic ADL without needing assistance (Galvin, 2012; Gold, 2012).
  - Inability to perform IADL typically precedes inability to perform basic ADL (Galvin, 2012).
  - Inability to manage finances may be one of the earlier IADL changes suggestive of dementia (Gold, 2012).

Visual Perception, Language Skills, Sensory Impairments

Normal aging leads to changes in all 5 senses:

- Visuoperceptual difficulties (Macknik et al., 2016; Staudinger et al., 2011; NEI, n.d.)
- Auditory problems (Tun et al., 2012)
- Speech and language impairments (Sörös et al., 2009; Tun et al., 2012)
- Changes in taste (NIA, n.d.)
- Changes in smell (Vasavada et al., 2015)



Dementia: Overview

- Dementia is a general term encompassing a variety of neurodegenerative diseases and conditions that cause progressive cognitive and behavioral impairments affecting ADLs (Cooper & Greene, 2005).
  - Chronic and persistent, with no cure
  - Caused by damage to brain cells
  - Type of dementia and symptoms depend on which regions of the brain are damaged.
- Dementia is not part of the normal aging process.
- Some symptoms of dementia are potentially caused by treatable conditions (Downing et al., 2013; Galvin et al., 2012; Hildreth et al., 2015).

Dementia: Overview, continued

- Estimates of prevalence and incidence in the United States vary by age and other factors.
  - Global prevalence of all-cause dementia is between 5% and 7% among adults ages 60+ (Prince et al., 2013).
  - Prevalence of dementia increases with increasing age to up to 37.4% of persons aged 90 and older (Plassman et al., 2007), with an incidence of 33.3 (SE, 4.2) per 1,000 person-years (Plassman et al., 2011).
    - Incidence of cognitive impairment, not dementia (CIND), was 60.4 (SE, 7.2) per 1,000 person-years.
    - 120.3 (SE, 16.9) individuals/1,000 person-years progressed to dementia.

Dementia: Overview, continued

- Emerging evidence indicates a possible decline in dementia prevalence worldwide (Christensen et al., 2013; Matthews et al., 2013; Satizabel, 2016).
- Survival after diagnosis of dementia depends on age at diagnosis (Rait et al., 2010).

Diagnosing Dementia

- Dementia is defined as a “significant deterioration in 2 or more areas of cognitive function that is severe enough to interfere with a person’s ability to perform everyday activities” (NINDS, 2017a).
- Diagnosis of dementia requires impairment in 2 or more core mental functions (NINDS, 2017a).
    - Memory
    - Language skills
    - Visual perception
    - Ability to focus and pay attention
    - Ability to reason and solve problems
- The loss of brain function is severe enough that a person has difficulty performing normal everyday tasks (including IADLs and ADLs) (NIA, n.d.).

Dementia and Memory

- Not every type of dementia initially manifests with memory impairment.
  - There are differences in memory impairments by types of dementia (Schubert et al., 2016).
  - The type of memory affected depends on the location of the brain cell damage (Kuceyeski et al., 2011).
- Initial memory impairment occurs in short-term/working memory and semantic memory (Wilson et al., 2011).
- Long-term memory is often retained until late-stage dementia (UCSF Memory and Aging Center, 2018a).

Dementia and Intellectual Disability

- Dementia of various types occurs at the same frequency in adults with intellectual disability (ID), except in adults with Down syndrome (DS).
- Dementia in adults with ID show some differences:
  - Some adults with ID have earlier onset and shorter duration
  - Symptom presentation at onset may differ
  - Standard screening tests may not be appropriate – ID oriented tests require comparisons over time of the same individual
- Adults with DS are at high risk for Alzheimer's disease and then Alzheimer's dementia
  - Early onset occurs in adults with DS – generally in early 50s
  - Most adults with DS survive less than 7 years after onset
- Early symptoms of dementia in adults with DS may manifest differently
  - Loss of sociability – a noticeable change in personality
  - Abrupt onset of seizures
  - Incontinence when toileting skills had been intact
  - Sleep/wake cycle changes or disruptions

Dementia and Visual Perception and Sensory Impairments

- Impairments may result from normal aging and/or from progressive damage to the brain (Roberts et al., 2016).
- Normal aging typically leads to mild visual problems, as well as increasing the risk for specific visual conditions.
- Each type of dementia can affect visuoperceptual abilities differently, including (Possin, 2010):
  - Visuoperceptual difficulties (such as visual hallucinations) (Auning et al., 2011)
  - Auditory problems (such as auditory hallucinations)
  - Tactile changes
  - Changes in taste (seen in frontotemporal degeneration).
  - Changes in smell (Roberts et al., 2016)

Dementia and Impairments in ADLs

- Dementia is characterized by cognitive impairments that eventually lead to loss of ability to perform ADLs (Verlinden et al., 2016).
- Persons living with early-stage dementia have difficulties first with IADLs.
- As the dementia progresses to middle and late stages, PLwD lose ability to perform basic ADL (Verlinden et al., 2016).
- Functional consequences of cognitive impairments are key components of a diagnosis of dementia (NIA, n.d.).

Behavioral and Psychological Symptoms of Dementia (BPSDs)

- In addition to cognitive and functional impairments, PLwD may manifest any of these neuropsychiatric and behavioral consequences (Aarsland et al., 2014; Desai et al., 2012; Kales et al., 2015):
  - Mood disorders: Apathy, depression, dysphoria
  - Sleep disorders:
    - Insomnia, hypersomnia, circadian rhythm disorders
    - Obstructive sleep apnea
  - Psychotic symptoms: Delusions, hallucinations
  - Agitation: Pacing, wandering, sexual disinhibition, aggression, anxiety

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Mild Cognitive Impairment

- MCI is becoming one of the most common clinical manifestations of older people, as compared with specific dementias (Etgen, et al., 2011; Mufson et al., 2012; Pistacchi, et al., 2015).
- MCI is usually marked by problems with memory, language, judgment, and thinking—problems greater than expected for the age of the person, but less than is required for dementia diagnosis (Arevalo-Rodriguez et al., 2016; Brown et al., 2011; Stewart, 2012).
  - The person with MCI can still carry out everyday activities.
  - Symptoms may be noticeable to family/friends.

MCI, continued

- Not all MCI progresses to dementia. Some persons with MCI can return to normal cognitive abilities instead of progressing to dementia (Ganguli et al., 2011; Koepsell et al., 2012; Pankratz et al., 2015).
- When MCI does progress to dementia, it may progress to any of the ADRD—Alzheimer's disease, Parkinson's disease dementia, frontotemporal degeneration, or vascular dementia (Etgen et al., 2011; Jicha et al., 2010; Mufson et al., 2012; Pistacchi et al., 2015; Yoon et al., 2014).
- From a clinical perspective, MCI is most likely first detected in primary care, although the symptoms may be overlooked and minimized (Olazaran et al., 2011).
  - No treatment for MCI (Langa & Levine, 2014)
- MCI progresses to dementia at a rate of approximately 10–20% a year (Etgen et al., 2011; Langa & Levine, 2014).

MCI, continued

- Data from Mayo Clinic Study of Aging have identified some factors that may be predictive of MCI: self-reported memory concerns, history of stroke or atrial fibrillation, alcohol problems, diabetes (Pankratz et al., 2015).
- Treatable predictors (or risk or prognostic factors) associated with MCI include diabetes, prediabetes, metabolic syndrome, hypertension, hyperlipidemia, low dietary folate, chronic alcohol abuse, and possibly chronic renal failure (Cooper et al., 2015; Etgen et al., 2011; NIAAA, 2001).
- Treating some predictors could potentially decrease the incidence of MCI conversion to dementia (Cooper et al., 2015; Etgen et al., 2011).
- 50% of persons with MCI versus 25% of cognitively normal persons in the Mayo Clinic Study of Aging also had non-psychotic symptoms—particularly apathy, agitation, anxiety, irritability or depression (Geda et al., 2008).
    - Neuropsychiatric symptoms may increase the risk of conversion from MCI to dementia (Cooper et al., 2015; Stella et al., 2014).
- Psychosis in MCI is more likely associated with severe frontal lobe symptoms versus Alzheimer's disease; it can occur in both (Van der Mussele et al., 2015).

MCI and Depression

- Depressive symptoms occur in up to 63% of persons with MCI (Panza et al., 2010).
- Depressive symptoms may hasten conversion from MCI to Alzheimer's disease (AD) (Goveas et al., 2011; Mourao et al., 2015; Royall et al., 2013).
- History of depression (especially early-onset depression) increases the risk of developing AD (Baba et al., 2011; Royall et al., 2013; Richard et al., 2013).
- Research suggests that effective management of depression may be a possible intervention target for MCI and possibly dementia (Mourao et al., 2015).

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ADRD: Overview

- Alzheimer's disease is the most common and most well-known of the types of dementia (NIA, 2016, 2017a).
- There are numerous other types of dementia.
  - Some have similar manifestations, but not necessarily in the same order of appearance as with Alzheimer's disease.
  - Other forms may have different underlying etiologies.
  - Dementia can have a combination of causes—"mixed" dementia.
    - Alzheimer's disease and vascular dementia is the most common "mixed" dementia

Alzheimer's Disease: Prevalence and Demographics

- AD is the most common type of dementia in people over age 65.
  - AD accounts for 60–80% of cases of dementia (NIA, 2016, 2017a)
- It affects at least 5.7 million Americans (Alzheimer's Association, 2018; Hebert et al., 2003; Mitchell, 2015).
- By 2050, the number is expected to more than double due to the aging of the population (Alzheimer's Association, 2018).
- It affects approximately 200,000–250,000 people younger than 65 (Alzheimer's Association, 2018; Mitchell, 2015).
- Starting at age 65, the risk of developing AD doubles every 5 years. By 85+ years and older, the risk reaches nearly 50% (Alzheimer's Association, 2018).

Early-Onset Dementia (EOD)

- AD usually occurs in individuals who are age 65 and older (NIA, 2017b).
- EOD occurs in people ages 30–65.
  - There is disagreement regarding upper age limit for EOD.
  - EOD represents up to 5% of cases of AD (NIA, 2017b).
    - Some cases of EOD have no known cause.
    - Many cases are inherited, called familial Alzheimer's disease (FAD) (NIA, 2017b).
  - EOD is associated with 3 known genetic mutations: amyloid precursor protein, presenilin 1, and presenilin 2 (NIA, 2017b; Wu et al., 2012).
- Early-onset dementia occurs also in adults with Down syndrome
  - Mean age of onset is in early 50s (Janicki & Dalton, 2000; Sinai et al. 2017) due to precocious aging.
  - Cause of AD is due to presence of an extra copy of chromosome 21 that carries the gene which produces the amyloid precursor protein (APP) (NIA, 2017).

Nongenetic Risk Factors for Alzheimer's Disease

- Etiology of AD not yet known
- Many different hypotheses for non-inherited forms
- "Risk" factors for non-inherited forms of AD:
  - Advancing age (Alzheimer's Association, 2018)
  - Cardiovascular and metabolic syndrome risk factors (Cheng et al., 2012; Ascher-Svanum et al., 2015; De la Monte, 2012; Cermakova et al., 2014)
  - Head trauma, especially recent traumatic brain injury (TBI) (Gilbert et al., 2014)

Genetic Mutations Associated With Alzheimer's Disease

- A family history with an affected first-degree relative increases the risk of late-onset AD (NIA, 2017b).
  - Risk further increases with each additional first-degree relative affected (NHGRI, 2013).
  - Having specific apolipoprotein E (APOE) gene mutations increases the risk of AD (Baranello et al., 2015; Galimberti & Scarpini, 2010; NIA, 2017b; Tang & Gershon, 2003).
- Specific genetic mutations in early-onset AD:
  - 3 most common genetic mutations involve gene for amyloid precursor protein (APP), presenilin 1 (PS1), and presenilin 2 (PS2) proteins (NIA, 2017b; Wu et al., 2012).

Genetic Mutations Associated With Alzheimer's Disease, continued

- People who inherit any of these genetic mutations are at high risk of developing AD (Baranello et al., 2015; Galimberti et al., 2010; NIA, 2017b; Tang et al., 2003).
  - There is a significant association between general fluid cognitive function and 4 genes associated with AD: TOMM40, APOE, ABCG1, MEF2C (Davies et al., 2015).

Pathophysiology of Alzheimer's Disease

- Major hypotheses linking changes in the brains of AD patients with disease symptoms are:
  - Cholinergic hypothesis (Wesson Ashford, 2015)
  - Amyloid hypothesis (Querfurth & LaFerla, 2010)
  - Tau hypothesis (Hampel et al., 2015)
- Beta amyloid plaques and neurofibrillary tangles have key roles in the pathogenesis of AD (Baranello et al., 2015).
  - Severity of cognitive impairment is associated more with the burden of neocortical neurofibrillary tangles (Nelson et al., 2012).

Role of APOE

- Genetic testing not generally recommended outside of clinical trials
- 3 common forms of APOE: ε2, ε3, and ε4 (NIA, 2015b)
- APOE ε3: the most common allele; apparently has a neutral role—neither decreases nor increases the risk of Alzheimer's disease (NIA, 2017b)

Role of APOE, (continued)

- APOE ε4: primarily responsible for transporting cholesterol and lipids in the blood; may play a role in amyloid clearance (NIA, 2017b)
- The APOE ε4 allele has been shown to increase the risk for late-onset AD, age-related cognitive decline (Alexander et al., 2012), and Lewy body dementia (LBD) (Berge et al., 2014).
  - According to the National Human Genome Research Institute (2013), a person who inherits the *APOE4* allele from only one parent has a 3-fold increase in load risk, whereas a person that inherits *APOE4* from both parents is 10 times more likely to develop AD (Rhinn et al., 2013).
  - Having parental family history of AD along with the APOE4 allele is associated with possible precursors to AD (Adluru et al., 2014).
  - People with mixed AD/LBD (see discussion on LBD in upcoming slides) dementia have a different clinical phenotype vs. persons with only AD (Chung et al., 2015).
  - APOE status also appears to influence the effect of depression on AD (Karlsson et al., 2015).
  - Having only 1 ε4 allele increases all-cause mortality by ~77% compared with non-carriers (Beydoun et al., 2013).

Role of APOE, (continued)

- In contrast, APOE ε2 genotype:
  - Is associated with delaying onset of AD and LBD (Berge et al., 2014)
  - Protects against functional decline in amnestic MCI (aMCI) and AD (Bonner-Jackson et al., 2012; Conejero-Goldberg et al., 2014)

Diagnosing Alzheimer's Disease

- Diagnosis is predominantly made by PCP, geriatrician, neuropsychologist, or neurologist based on:
  - Physical and neurological examinations
  - Person's medical and family history, psychiatric history, and history of cognitive and behavioral changes
  - Informant substantiation and reports
- Some cases may need referral for imaging or more extensive cognitive testing.
- Cerebrospinal fluid (CSF) biomarkers are used only in research (Ferreira et al., 2014).

The Progression to Alzheimer's Disease Dementia

- Original diagnostic criteria for Alzheimer's disease: significantly revised in 2011 by the National Institute of Aging (NIA) in conjunction with the Alzheimer's Association (AA) based on the greater understanding of the disease (Albert et al., 2011; Jack et al., 2010, 2011; McKhann et al., 2011; Sperling et al., 2011).
- New consensus criteria: two substantial changes (Albert et al., 2011; Jack et al., 2010, 2011; McKhann et al., 2011; Sperling et al., 2011):
  - Recognition of 3 stages of Alzheimer's disease:
    - Preclinical stage that occurs before any changes in cognition or functional impairments can be detected
    - Mild cognitive impairment (MCI) due to Alzheimer's disease, in which there is cognitive impairment but day-to-day function is not impaired
    - Dementia due to Alzheimer's disease, in which day-to-day function is impaired (Jack et al 2011)
  - Incorporation of biomarkers (currently limited to research purposes) (Jack et al., 2010)

Stages of Alzheimer's Disease Dementia

Dementia of Alzheimer's disease has been described as progressing through three stages (NIA, 2017a; Sona et al., 2013):

- Early or mild stage, during which the clinical symptoms include mild cognitive decline and functional impairments
- Middle or moderate stage, during which there are moderate impairments
- Late stage or severe (or end-stage) Alzheimer's disease, with severe manifestations

Progression and Mortality

- Progressive neurodegeneration with increasing impairments
- Mortality:
  - 6th leading cause of all deaths in the United States (Heron et al., 2009)
  - 5th leading cause of death for people ages 65 and older (Heron et al., 2009)
  - Time from diagnosis to death as little as 3 to 4 years if PLwD >80, but as long as 10+ years in younger person (NIA, n.d.)
- In 2013, more than 84,000 Americans died from AD, but another 700,000 are expected to die WITH Alzheimer's (i.e., die of other causes after developing the disease) (Alzheimer's Association, 2018).

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Vascular Dementia (VaD): Overview, Prevalence, and Demographics

- Vascular dementia (VaD) is another common form of dementia (NIA, n.d.; O'Brien & Thomas, 2015).
- VaD results from a blockage or reduction in blood flow—usually from a stroke or a series of strokes—that deprives oxygen and nutrients to brain cells, damaging the cortex of the brain (associated with learning, memory, language):
  - Subcortical (ischemic) vascular dementia (Roh & Lee, 2014)
  - Stroke-related VaD
  - Mixed VaD with AD: autopsy results show a majority of PLwD over age 80 likely had mixed dementia (NIA, n.d.)
- Rates of dementia, especially VaD, are steadily decreasing (Satizabal et al., 2016).
  - Decrease in most vascular risk factors, except diabetes and obesity, possibly associated with greater recognition/management in primary care setting (Satizabal et al., 2016)

VaD Medical and Lifestyle Risk Factors

Persons may have specific medical conditions that increase their risk of VaD:

- Cardiovascular diseases (De Bruijn et al., 2015)
- Diabetes mellitus, hyperglycemia, insulin resistance, and metabolic syndrome (Biessels et al., 2014; Karter et al., 2015)
- Cerebrovascular diseases, systemic lupus erythematosus, temporal arteritis, and brain hemorrhage
- Chronic kidney disease and amyloid angiopathy
- Prior stroke or heart attack—each independently associated with an increased risk of Alzheimer's disease and vascular cognitive impairment (Sahathevan et al., 2011)

VaD Medical and Lifestyle Risk Factors, continued

- Hypertension (50%) and stroke (Wiesmann, et al., 2013)
  - Early treatment of hypertension can reduce VaD risk and slow progression (Baskys et al., 2012)
- Several lifestyle risk factors have been associated with an increased risk of vascular dementia:
  - Obesity
  - Smoking
  - Lack of physical activity or exercise
  - Lack of social support
  - An unhealthy diet

VaD Clinical Manifestations

- Manifestations: diverse and related to the areas of the brain affected (Jellinger & Attems, 2010)
- Challenging to identify VaD (compared with other types such as AD) unless there is evidence of a temporal relationship with a cerebrovascular event (Attems & Jellinger, 2014; Biessels, 2015; McGuinness et al., 2010)
- Cortical vs. subcortical syndromes:
  - Cortical VaD symptoms vary by original stroke location.
  - Subcortical VaD manifests with focal motor signs, gait disturbance, personality/mood changes, and cognitive syndrome with mild memory deficits, psychomotor retardation, and abnormal executive function.
- Symptoms generally similar to those of other types of dementia
- Stepwise progression often in symptoms of cortical VaD

VaD Symptoms

Many symptoms of vascular dementia are similar to those seen in persons with Alzheimer's disease (Mayo Clinic, 2018; Moretti et al., 2015; Noh et al., 2014):

- Cognitive symptoms
- Emotional symptoms
- Hallucinations, delusions
- Physical difficulties

VaD Progression and Mortality

- Speed of progression varies by person and vascular risk factors (Blom et al., 2013)
- Impairments progress with each additional stroke or vascular insult.
- Progress may be in steps, with plateaus followed by periods of rapid deterioration.
- Persons with VaD decline at a slower rate than persons with AD (Gill et al., 2013).
- Lifespans of people with VaD after diagnosis: 3 to 5 years after symptoms begin (Brodaty et al., 1993; Wolfson et al., 2001) (fewer years than with AD) (Xie et al., 2008; Helzner et al., 2008)

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LBD Overview: Dementia with Lewy Bodies and Parkinson's Disease Dementia

- Lewy body dementia (LBD) covers 2 related conditions—dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD) (Zweig et al., 2014).
- The defining features of LBD include motor Parkinsonism and cognitive impairments (Zweig et al., 2014; Aarsland, 2016; Connolly & Fox, 2014).
- Timing of dementia onset distinguishes between DLB and PDD (Mrak & Griffin, 2007; McKeith et al., 2005; Aarsland, 2016).
- Diagnosis of LBD is challenging, even among experts (Karantzoulis & Galvin, 2013; Zweig et al., 2014).
- LBD, Parkinson's disease (PD), and AD have many genetic similarities (Guerreiro et al., 2015).
  - However, differences in phenotypes have clinical implications (Chung et al., 2015).
  - Location of Lewy bodies also influences disease manifestations (ACT on Alzheimer's, 2012; Yoon et al., 2014; Aarsland, 2016).

LBD: Prevalence and Demographics

- Prevalence estimated at 1.3 million cases of LBD in the United States (Zweig & Galvin, 2014; Savica et al., 2013)
- Reportedly high number of underdiagnosed and frequently misdiagnosed cases (LBDA, 2013)
- Difficult to estimate prevalence of DLB separately from PDD
- Affects up to 5% of elderly people and up to 30% of all dementia cases (Karantzoulis & Galvin, 2013)

DLB: Incidence and Prevalence

- Accounts for 4.2% of all community-diagnosed dementia, with incidence of 3.8% of new dementia cases (Vann Jones & O'Brien, 2014)
- Affects more men than women and increases in incidence with age (LBDA, 2013)
- Affects people at a younger age than does PDD (LBDA, 2013)

PDD: Incidence and Prevalence

- PD affects about 1 million Americans (ACT on Alzheimer's, 2012).
- The percentage of people with PDD increases with increasing duration of PD.
  - Approximately 80% of patients with PD will eventually develop PDD (Russell et al., 2014).
- 15–20% of persons with PD have MCI, which is associated with a poor quality of life and more severe motor symptoms (Lawson et al., 2014; Aarsland, 2016).
- PD incidence increases with age (Pringsheim et al., 2014).
- PD rates differ among different races (Wright Willis et al., 2010).
- Incidence of PD is higher in specific ethnicities—Asians, Europeans, North Africans, North and South Americans—but highest among Ashkenazi Jews (Gan-Or et al., 2015).

LDB/PDD Risk Factors

- In general, there are few risk factors for LBD: Male, older than age 60, and possible genetic predisposition (Mayo Clinic, 2017a).
- An important risk factor for PDD is duration of PD. Probability of developing PDD is approximately 80% with extended time since PD diagnosis (Connolly & Fox, 2014).
- Other (nonspecific) risk factors for PDD include “atypical” Parkinsonian features, specific medical problems, non-motor symptoms, and rapid eye movement (REM) sleep behavior disorder (RBD) (Connolly & Fox, 2014; Desai et al., 2012; Bombois et al., 2010).

LBD Symptoms

- The defining features of LBD include motor Parkinsonism and cognitive impairments (Aarsland, 2016).
- Clinical manifestations of DLB and PDD are initially different but become more similar as the disease progresses.
- Comparison of DLB versus AD found some similarities and numerous differences (Auning et al., 2011; Tarawneh & Galvin, 2007; Karantzoulis & Galvin, 2013).
- Hallmark symptoms in early-stage PDD are movement related (Miller & Boeve, 2011) and also include:
  - Cognitive impairments
  - RBD, visuoperceptual changes, and depression
  - However, memory intact throughout most of the stages of PDD (ACT on Alzheimer's, 2012)
- Greater impairments are associated with DLB than with PDD (Yoon et al., 2014; Jicha et al., 2010).

LBD Progression and Mortality

- The prodromal stage is characterized by dysautonomia, olfactory dysfunction, RBD, and psychiatric symptoms that are apparent years before onset of dementia (possibly decades earlier with DLB) (Fujishiro et al., 2015).
- Far less is known regarding progression of LBD compared with knowledge on Alzheimer's disease. The Lewy Body Disease Association (LBDA) estimates an average duration of 5 to 7 years, with a range from 2 to 20 years. (LBDA, 2013)
- Survival time is shorter in DLB compared with Alzheimer's disease (Stubendorff et al., 2011).
- Men with DLB have increased mortality versus men with AD (Williams et al., 2006).

Outline

- Normal aging versus dementia
- Mild cognitive impairment
- Types of dementia: Alzheimer's disease and related dementias (ADRD)
  - Alzheimer's disease
  - Vascular dementia
  - Lewy body dementia
  - **Frontotemporal degeneration**
  - Other rare causes of dementia

Frontotemporal Degeneration (FTD): Overview and Prevalence

- Frontotemporal degeneration (FTD) is also known as frontotemporal disorder, frontotemporal dementia, or frontotemporal lobar degeneration (FTLD).
- FTD is a heterogeneous group of diseases with overlapping clinical symptoms but different causative genes and differing underlying pathologies (Lashley et al., 2015; Riedl et al., 2014).
- Generally rapid progression is associated with damage to the frontal and/or temporal lobes (Piguet et al., 2011), but memory networks are spared.
- Imaging studies may show possible evidence of tau (Pick bodies), TAR DNA-binding protein 43 (TDP43), or fused in sarcoma protein (FUS) inclusions (Mackenzie et al., 2011).

FTD: Overview and Prevalence, continued

- FTD usually affects younger people (<60 years).
  - 2nd most common cause of EOD after AD (Piguet et al., 2011)
  - ~60% diagnosed with FTD between ages 45 and 64 (Lashley et al., 2015; Riedl et al., 2014)
- Prevalence is estimated at approximately 15–22/100,000, with equal gender distribution (Lashley et al., 2015; Riedl et al., 2014).
- Between 50,000 and 60,000 Americans are affected.

FTD Types

- There are at least 3 distinctive clinical syndromes, each with heterogeneous neuropathology (NIA, 2017b).
  - Progressive behavior/personality decline: behavioral variant FTD (bvFTD)
  - Progressive language decline: Primary progressive aphasia (PPA)
  - Progressive motor decline: corticobasal syndrome, amyotrophic lateral sclerosis, or supranuclear palsy
- Behavioral variant FTD (bvFTD) is the most common variant. It is characterized by marked personality changes and changes in social conduct (Borroni et al., 2015; Mioshi et al., 2010).

FTD Types, continued

- Primary progressive aphasia (PPA) is subdivided into 3 different syndromes, all (at least initially) mostly language related (Mioshi et al., 2010).
  - Semantic dementia (sFTD)
  - Progressive non-fluent aphasia (PNFA) (Mioshi et al., 2010; Piguet et al., 2011)
    - Some patients with PNFA develop full-blown corticobasal syndrome as the disease progresses (Mioshi et al., 2010).
  - Progressive logopenic aphasia (PLA) (Kremen et al., 2011)
- FTD with progressive motor decline is rare (NIA, 2017b).
- FTD is challenging to diagnose (Pose et al., 2013), but there are recent diagnostic criteria (Rascovsky et al., 2011).

Manifestations of FTD Variations

- bvFTD is characterized by progressive behavioral and personality decline (NIA, 2017b).
- PPA variations are characterized by progressive language decline, including impaired ability to speak, understand, read, and write (NIA, 2017b).
  - Can develop full-blown corticobasal syndrome as the disease progresses (Mioshi et al., 2010)
- FTD with progressive motor decline can involve movement problems/ slowed movement, muscle rigidity (Parkinsonian symptoms), body stiffness, and changes in behavior or language.
- Persons with FTD can have various difficulties with physical movement but can retain the ability to perform ADLs.

FTD Pathophysiology and Genetic Risk Factors

- 15–40% of persons with bvFTD have a family history of dementia (NIA, 2017b).
- 10–30% of persons with FTD show an autosomal dominant pattern of inheritance (NIA, 2017b).
  - It is important to discuss family history in persons with FTD (UCSF Memory and Aging Center, n.d.; Fu et al., 2012; Piguet et al., 2011; Riedl et al., 2014).
  - A common feature of FTD is the accumulation of certain neuronal proteins (Baizabal-Carvallo & Jankovic, 2016).
    - Most important: Microtubule-associated protein tau (MAPT, also called tau gene), transactive response DNA-binding protein (TARDBP), and the fused in sarcoma protein (FUS)
  - Generally, persons with MAPT mutations have an early age of onset (<65 years), whereas those with granulin (GRN) mutations have later onset.

Symptoms of bvFTD

- Characterized by disinhibition, apathy, and stereotypic (ritualized) behaviors (Ferrari et al., 2011; Piguet et al., 2011)
- Changes in behavior and personality, language problems, and motor problems (NIA, 2017b; Ferrari et al., 2011)
  - Blunting of affect and apathy; lability, anxiety, irritability, and euphoria also common (Piguet et al., 2011; Ferrari et al., 2011)
  - Increasing social isolation (Piguet et al., 2011)
  - Depression in up to 40% of persons with bvFTD (Ferrari et al., 2011)
- Minimal memory impairment in early stages (Arlt, 2013; Schubert et al., 2016)
- Lack of insight (understanding, acknowledgment) of their unusual behaviors (Piguet et al., 2011)
- Possible binge eating habits (Piguet et al., 2011; Ferrari et al., 2011)
- Psychotic features uncommon (Piguet et al., 2011)

FTD Progression and Mortality

- Patients with bvFTD have greater disease severity and a faster progression through the clinical stages vs. patients with the language variants of FTD (Mioshi et al., 2010; Piguet et al., 2011).
  - Language impairment at diagnosis associated with shorter survival (Garcin et al., 2009)
  - Later age of onset associated with faster disease progression (Chow et al., 2012)
- FTD may progress more rapidly than AD (Roberson et al., 2005).
- People generally live 3–10 years after diagnosis (5–8 years after symptoms first appear) (Garcin et al., 2009; Hodges et al., 2003; Riedl et al., 2014).

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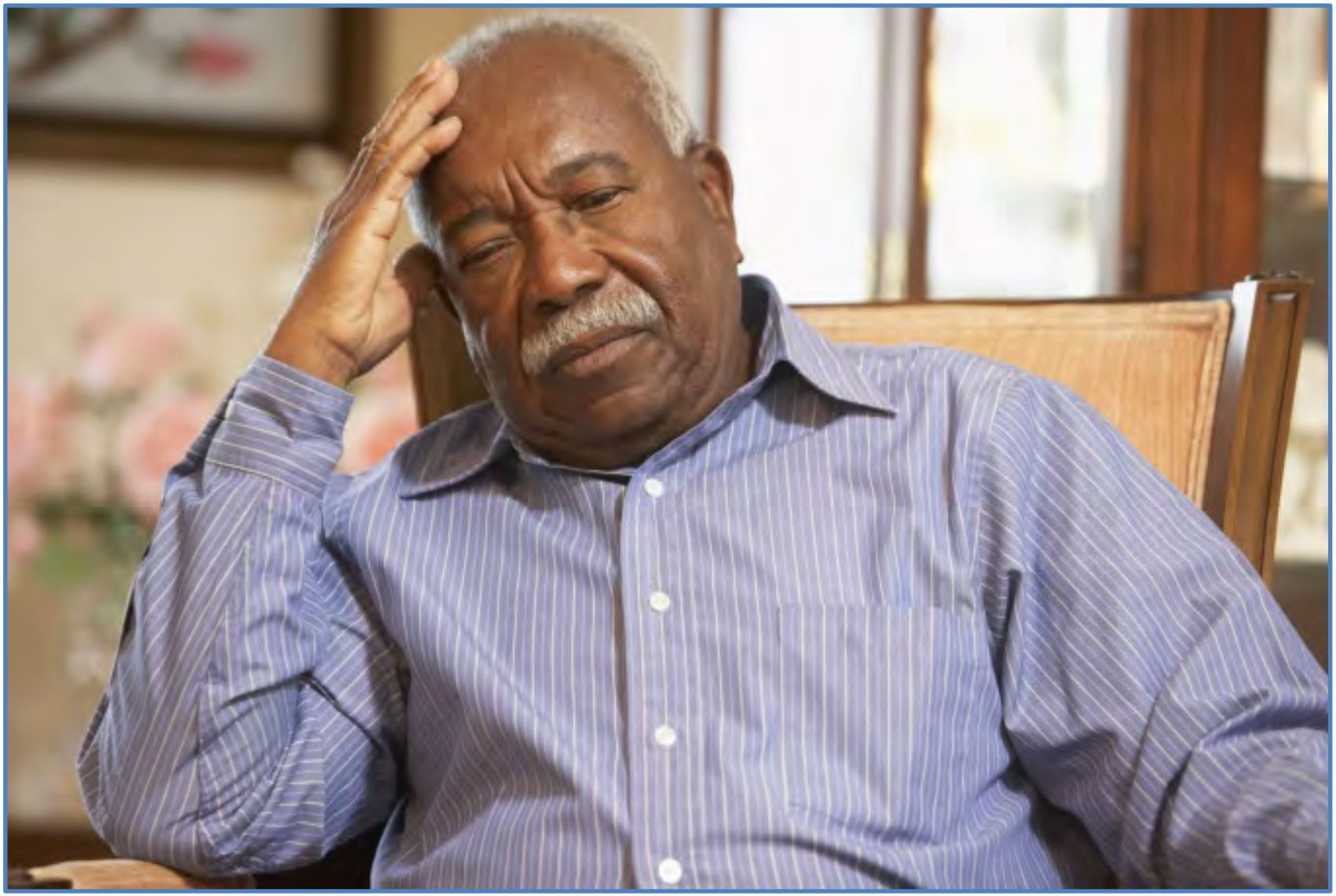
Other Causes of Dementia

- Creutzfeldt-Jakob disease
- Neurodegenerative diseases, such as Huntington chorea (Mielcarek, 2015) and multiple system atrophy
- Sporadic cerebral amyloid angiopathy (CAA)—important cause of spontaneous intracerebral hemorrhage and cognitive impairment in elderly (Charidimou et al., 2012)
- Normal pressure hydrocephalus (NINDS, 2017b)
- HIV-associated neurocognitive disorders (HAND)—including AIDS-dementia complex (ADC) and HIV-associated dementia (HAD) (Heaton et al., 2010)



Evaluation

1. **The most notable difference between changes associated with normal aging and those associated with dementia is:**
   a. Only persons living with dementia have problems with memory and attention.
   b. A high level of depression and anxiety is more likely to be observed in persons living with dementia.
   c. Persons living with dementia have severe enough mental decline so as to interfere with daily life.
   d. Visual and other perceptual impairments are most likely to be signs of normal aging than neurodegenerative disease.

Evaluation (continued)

2. **All but which of the following are considered to be a common type of dementia?**
   a. Alzheimer's disease
   b. Huntington's disease
   c. Lewy body dementia
   d. Vascular dementia

3. **Which of the following is not a risk factor for vascular dementia?**
   a. Smoking
   b. Obesity
   c. Lack of social support
   d. Heart-healthy diet

Evaluation (continued)

4. Which of the following statements is true?

a. Imaging studies and laboratory tests can identify a person's stage of dementia.

b. There are clear signs and symptoms that distinguish between the stages of dementia.

c. All persons with early-stage dementia manifest with memory impairment.

d. The rate of progression through the stages of dementia depends upon the underlying cause of dementia.

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