

**Evaluation and Management of Alzheimer's Dementia and related disorders: What is new in 2019?**

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**Objectives**

- To differentiate amongst the most common causes of dementia and understand diagnostic criteria and standard clinical evaluation.
- To determine effective and safe treatments for the cognitive, functional and behavioral symptoms of dementia.
- To appreciate current research approaches for disease modifying therapies to treat Alzheimer's dementia.

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**2019 Alzheimer's Disease Facts & Figures**

Alzheimer's Association (2019)

**2019 ALZHEIMER'S DISEASE FACTS AND FIGURES**

ALZHEIMER'S DISEASE IS THE **6<sup>TH</sup>** leading cause of death in the United States

**58** million Americans are living with Alzheimer's. **14** million more are newly projected to have Alzheimer's by 2050.

**82%** of seniors say it's important to have their thinking or memory checked.

**BUT ONLY 16%** of seniors receive regular cognitive assessments.

**MORE THAN 16 MILLION** Americans provide unpaid care for people with Alzheimer's or other dementia. These caregivers provided an estimated **18.5 BILLION HOURS** valued at nearly **\$234 BILLION**.

**EVERY 65 SECONDS** someone in the United States develops the disease.

**9%** between 2003 and 2017 deaths from heart disease have decreased, while deaths from Alzheimer's disease have increased **145%**.

**1 IN 3** seniors dies with Alzheimer's or another dementia. It kills more than breast cancer and prostate cancer **COMBINED**.

**IN 2018**, Alzheimer's and other dementia will cost the nation **\$290 BILLION**. **BY 2050**, these costs could rise as high as **\$1.1 TRILLION**.

alzheimer's association

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**The challenge began 100+ years ago** 

- November 1906: Dr. Alois Alzheimer presented first case in Germany
- 51-year-old Auguste D. had profound memory loss, confusion, language difficulty, unfounded suspicions about husband and hospital staff
- On autopsy: plaques and tangles, brain shrinkage, vascular changes
- Her young age made Alzheimer think Auguste had a rare disease associated with middle age

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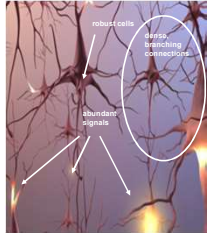
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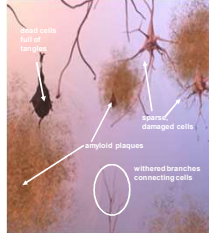
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**Pathology: Amyloid plaques** 

**Healthy Neurons**



**Alzheimer's Neurons**



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**Pathology: Tau tangles** 

Image of neurofibrillary tangles (NFTs) from Wikipedia

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**Risk Factors for Alzheimer’s Disease** 

- Age
- Genetics (APOE-4, Presenilin 1, 2 and APP)
- Down’s Syndrome
- Family History

Modifiable Risk Factors:

- Hypertension
- Diabetes
- Alcohol and Substance Abuse
- Depression
- Hyperlipidemia

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**Making the Diagnosis in the General Care Setting** 

**Initial Assessment**

- History from patient and family member/close friend
- Relevant medical history; medication review
- Lab values: TSH, vitamins B12 and D, folate, CBC/Chem20

**Screening for Memory Loss**

- Cognitive screen
- *Tools available on the Alzheimer’s Pocketcard App*
- Psychiatric screen

**Referral to a Specialist**

- Imaging to rule out other causes: CT, MRI
- Specialty referral: neurology, psychiatry, neuropsychology
- Specialized testing: FDG PET, Amyloid PET, CSF examination, APOE/genetic testing

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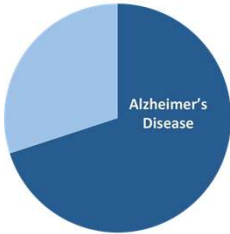
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**Types of Dementia** 

- Vascular Dementia
- Dementia with Lewy Bodies
- Parkinson’s Disease
- Frontotemporal Dementia
- Huntington’s Disease
- Creutzfeldt-Jakob Disease
- Normal Pressure Hydrocephalus (NPH)
- Physical Injury to Brain
- Down Syndrome Dementia
- Korsakoff’s Syndrome



Alzheimer’s Disease

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**Treatable Causes of Cognitive Decline** 

- Vitamin B12, Vitamin D and folate deficiency
- Hypothyroidism
- Unstable medical problems: diabetes, heart failure
- Normal Pressure Hydrocephalus (NPH)
- Medication side effects: Tylenol PM (acetaminophen plus diphenhydramine)
- Excessive alcohol consumption

*Image of Tylenol PM box with "See New Warning" on label*

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**Montreal Cognitive Assessment (MoCA)** 

**Purpose**

- Used to detect mild cognitive impairment or early cognitive decline in about 15 minutes
- Not designed to indicate the severity of cognitive impairment

**Contents**

- Consists of a 30 point scale, a score of 26 or above is considered "normal"
- Assesses eight major cognitive domains:

Visuospatial/ Executive	Naming	Memory	Attention
Language	Abstraction	Delayed Recall	Orientation

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**FDA Approved Therapies** 

Cholinesterase Inhibitors:

- Donepezil
- Rivastigmine
- Galantamine

Glutamatergic agents:

- Memantine

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Pharmacotherapy for AD 		
Drug name (Brand name) (stages) FDA clearance date	Dosage	Adverse effects (>10%)
Donepezil (Aricept) (all stages) FDA Approval: 1996	5 mg PO in AM; may increase to 10 mg after 4-6 weeks	Nausea, diarrhea, insomnia, accident, infection
rivastigmine (Exelon) (all stages) FDA Approval: 2000	<i>Pill:</i> Initial: 1.5 mg PO q12h Increase by 1.5 mg/dose q2 weeks Maintenance: 3-6 mg PO q12h  <i>Transdermal:</i> Initial: 4.5 mg/24h (not therapeutic) Mild-moderate: 9.5-13.3 mg/24h Moderate-severe: 13.3 mg/24h	Nausea, vomiting, dizziness, diarrhea, headache, anorexia, abdominal pain

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Pharmacotherapy for AD 		
Drug name (Brand name) (stages) FDA clearance date	Dosage	Adverse effects (>10%)
Galantamine (Razadyne) (mild to moderate) FDA Approval: 2001	<i>Initial</i> Conventional: 4 mg PO q12h ER: 8 mg PO qAM <i>Maintenance (titrate at min 4 week intervals)</i> Conventional: 8-12 mg PO q12h ER: 16-24 mg PO qAM	Nausea, diarrhea, vomiting
Memantine (Namenda) (moderate to severe) FDA Approval: 2003	<i>Tablet:</i> 5 mg PO once daily; increase by 5 mg/day each week to 20 mg/day PO qDay <i>ER:</i> 7 mg PO qDay; increase weekly to 28 mg PO	No AE over 10%: Dizziness (7%), confusion(6%), headache (6%)
Donepezil + Memantine (Namzaric) (moderate to severe) FDA Approval: 2014	memantine ER/donepezil: 28 mg/10 mg PO qDay  If stable on donepezil, titrate memantine by 7 mg increments	Nausea, diarrhea, insomnia, accident, infection

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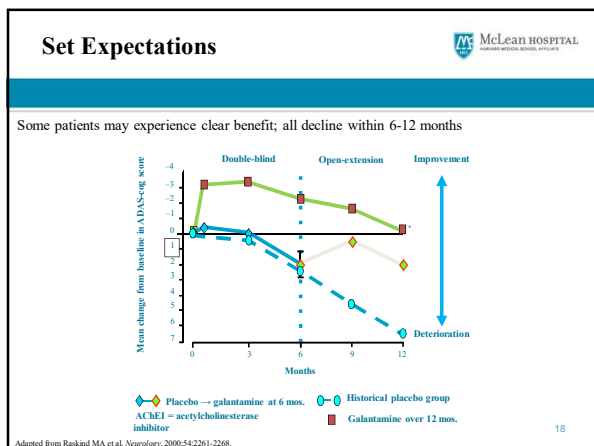
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**Causes of Behavioral and Psychological Symptoms of Dementia** 

- Environmental
  - Caregiver interactions, time of day, change in routine, noise, cultural issues
- Medical
  - Pain, infection, constipation, electrolyte disturbance, unstable medical illness, poor sleep
- Psychiatric
  - Prior history of psychiatric illness (depression, anxiety disorder, bipolar disorder, Substance Use Disorder)

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**Medication therapy for BPSD** 

- No FDA approved therapies
- Antipsychotics (APs) modestly effective at reducing symptoms, but this comes at the price of side effects (sedation, orthostatic hypotension, ataxia, parkinson's symptoms, Tardive Dyskinesia, metabolic syndrome, stroke risk and FDA warning for mortality)
- APA Consensus guidelines 2016 support short-term use of APs for severe agitation with psychosis not responding to behavioral interventions
- Other therapies include SSRIs (citalopram), mirtazapine and certain anticonvulsants but **NOT** benzodiazepines
- Experimental therapeutics for agitation
  - Dronabinol for AD with agitation (synthetic cannabinoid)
  - Electroconvulsive therapy (ECT) for severe agitation in AD

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**BPSD Management** 

- Non-pharmacologic strategies as first-line intervention:
  - Creating pleasurable or meaningful activities
  - Simplifying tasks
  - Enhancing communication
  - Very individualized
- Pharmacologic treatment of agitation and psychosis:
  - **Citalopram** 10-20 mg / **Escitalopram** 5-10 mg daily
  - **Risperidone\*** 0.5-2 mg daily
  - Aripiprazole\* 5-10 mg daily
  - Quetiapine\* 25-200 mg daily
  - Olanzapine\* 2.5 -10 mg daily

*\* \*Black box warning (increased mortality) and FDA warning (increased CVA risk) for all atypical antipsychotics*

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**Risk Management: Driving** 

- o Early AD increases:
  - Crash risk by as much as 7x
  - Risk of becoming lost while driving
- o Refer for road test:
  - MMSE < 24
  - MOCA < 18
- o Affects attention span, visual-spatial ability, sequencing, cognitive mapping

**Management Options:**

- o Counsel patient and care partner about risks
- o Physician reporting **voluntary** in MA
  - Advise patient to self-report serious impairment to RMV
  - Consider legal advice and report to RMV Medical Affairs Branch
- o Refer to AMA Ethical Opinion E-2.24
- o Refer to certified driving evaluator to avoid patient conflict

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**Risk Management: Capacity/Decision Making** 

- o Undue Influence / Elder Abuse
- o Vulnerability to Coercion
- o Finances
- o Medication
- o Decision Making
- o Home Safety
  - Cooking
  - Firearms

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**Risk Management: Wandering** 

- o Wandering and becoming lost is:
  - Common (60%)
  - Recurrent (75%)
  - Life threatening (40% mortality if not found)
  - Highly stressful for care partners
  - [medicalert.org/safereturn](http://medicalert.org/safereturn)

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**Advanced Care Planning** 

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- Living Will/Health Care Proxy
- Durable Power of Attorney
- Plan for changing care needs over course of disease
- Preferences for end-of-life care
  - Conversation Project Starter Kit for People with Dementia
- Care planning billable on CPT Code 99483
  - Billed in addition to extended E&M visit

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**Alzheimer's Association** 

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- Leading voluntary health organization in Alzheimer's care, support, and research
- Mission
  - Eliminate Alzheimer's disease through research
  - Provide and enhance care for all affected
  - Reduce risk of dementia through promotion of brain health
- 24/7 Helpline: 800-272-3900
- [www.alz.org](http://www.alz.org)

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**Current Research** 

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Biomarkers

Disease Modifying Therapeutics

Lifestyle Modification

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**All steps in  $\beta$ -amyloid production are potential targets**

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McLEAN MEDICAL SCHOOL AFFILIATE

- o Blocking the enzymes beta-secretase and gamma-secretase.
- o Administering a “vaccine” to help the body clear beta-amyloid from the brain.
- o Preventing beta-amyloid pieces from sticking together and forming plaques.

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**Aducanumab for MCI and Mild AD:  
Reduces amyloid plaque build-up in Brain**

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McLEAN MEDICAL SCHOOL AFFILIATE

Figure 1: Amyloid plaque reduction with aducanumab: example amyloid PET images at baseline and week 54.

Sevigny J et al. *Nature* 537, 50–56, 2016.

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**Clinical trials of disease-modifying therapies thus far ineffective**

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Image of the cover of The Boston Globe on Friday, March 22, 2019.  
Headline: “Another Alzheimer’s drug, another disheartening failure”

Two articles included: “In a business of highs and lows, biotech’s stock hits rock bottom” by Lary Edelman and  
“Caregivers’ hopes crushed as Biogen halts trials” by Felice J. Fryer and Jonathan Saltzman and Adam Feurstein

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**BAN2401** 

- Partnership between Eisai and Biogen
- Antibody targeting pre-plaque form of  $\beta$ -amyloid
- Phase 2b trial of 856 people
  - MCI due to AD
  - Mild AD
- Amyloid PET used to enroll and track results
- At highest dose tested:
  - 81% reverted from  $\beta$ -amyloid positive to negative
  - 30% reduction in rate of cognitive decline

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**Healthy Brain Aging:**  
Nutrition to Reduce Alzheimer's Risks 

- **Eating foods typical of "Mediterranean Diet" Reduces Risk of AD by 40%**  
(Columbia Univ. Scarmeas, Stern, Tang, Mayeux & Luchsinger 2006 & 2009)
- **DASH Anti-Hypertensive Diet Lowers Risk of Dementia;**  
Combination of Foods: Vegetables, Whole Grains, Nuts Legumes &, Low or No-fat Dairy (Wengreen et. al. - 3400 Utah seniors)
- **Nutrients, in combination, lowering risk:**
  - Nuts, fish, tomatoes, poultry, fruits, cruciferous & dark & leafy vegetables, salad dressing with oils, as well as, mono-unsaturated fatty acids, omega 3's, vitamin E, vitamin B12 & folate.
  - Low intakes of high-fat animal foods, i.e. dairy, red meat, organ meat and butter, and of saturated fats & Omega 6's (Columbia Univ. 4 year study of 2,148 New Yorkers -June 2010 Y.Gu, Scarmeas, et.al. Arch of Neurol)

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**Healthy Brain Aging:**  
Exercise May Reduce 'Senior Moments' 

- Exercise at mid-life reduces subsequent risk of dementia (Andel, 2008; 2. Gage 2002; 3. Rolland 2008)
  - Moderate-intensity walking regimen or a stretching/toning program
  - Resistance training like weight lifting, aerobic training like walking, or balance and tone exercises, twice weekly for six months
- Increases brain cell growth in animals
- Increases brain blood flow in humans

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### Sleep and Alzheimer's

McLean HOSPITAL  
VAHARB MEDICAL CENTER, AFFILIATE

- Sleep disordered breathing may speed up the progression of AD and Dementia
  - SDB has been found to be associated with higher levels of amyloid plaque and tau proteins in the brain
  - SDB may be a risk factor for AD
- SDB is treatable and early treatment could potentially delay the onset/progression of AD and All-cause Dementia
- Getting less than 7-8 hours of sleep a night has also been found to be associated with all-cause dementia
  - Getting the right amount of sleep may be a protective factor

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### The Lancet Commission 2017: 35% of all Dementia may be Preventable

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Early Life: Less Education

Mid-Life: Hearing Loss, Hypertension, Obesity

Late Life: Smoking, Social Isolation, Physical Inactivity, Diabetes, Late Life Depression

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### Research in Lifestyle Modification: SPRINT MIND

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- Hypertension
  - Sys BP >130 mmHg
- Additional CV risk factor
- Randomly assigned to
  - Standard: Systolic BP <140 mmHg
  - Intensive: Systolic BP <120 mmHg

	Intensive (n=4678)	Standard (n=4683)
Mean (SD) age, years	67.9 (9.4)	67.9 (9.5)
≥age 75	28.2%	28.2%
Female	36.0%	35.2%
White	57.7%	57.7%
African-American	29.5%	30.4%
Hispanic	10.3%	10.3%
Mean (SD) baseline BP		
Systolic	139.7 (15.8)	139.7 (15.4)
Diastolic	78.2 (11.9)	78.0 (12.0)

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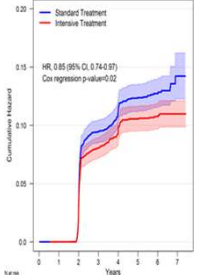
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**Research in Lifestyle Modification: SPRINT MIND** 

**Intensive treatment group:**

- o 19% reduction in MCI risk
- o 15% reduction in combined risk of MCI and dementia
- o Dramatic reduction in white matter lesions on MRI
- o Immediate opportunity with life changing potential



Standard Treatment: n=426  
Intensive Treatment: n=427

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**Research in Lifestyle Modification** 

**U.S. POINTER**  
alzheimer's association

Two-year lifestyle intervention trial to support brain health and prevent cognitive decline in older individuals at increased risk for dementia

- Physical Exercise
- Nutritional Counseling & Modification
- Cognitive & Social Stimulation
- Improved Self-Management of Health Status

\$20 million commitment from the Alzheimer's Association

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**Reducing Risk for Cognitive Decline** 

- Physical activity
- Nutrition
- Cardiovascular health
- Social engagement
- Quit smoking
- Sleep
- Formal education
- Avoid brain injury
- Cognitive training
- Manage stress

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**Resources for Keeping up with Current Trials**

McLean HOSPITAL  
PARTNERS MEDICAL SCHOOL AFFILIATE

- FDA.gov
- ClinicalTrials.gov
- alz.org/TrialMatch



To learn more:  
» Visit [alz.org/TrialMatch](http://alz.org/TrialMatch)  
» Email [TrialMatch@alz.org](mailto:TrialMatch@alz.org) or  
» Call 800.272.3900

alzheimer's association  
trialmatch  
— Alzheimer's

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**Summary**

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- Early diagnosis of dementia is critical, more so with aging of the population and advent of disease modifying therapies
- Current treatments for dementia focus on cognitive, functional and behavioral symptoms
- Goal of treatment to stabilize symptoms, enhance quality of life and support caregiver all in an effort to enhance independence
- Prevention trials underway

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**Contact Information**

McLean HOSPITAL  
PARTNERS MEDICAL SCHOOL AFFILIATE

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- Fax: 617-855-3246
- Email: [bforester@partners.org](mailto:bforester@partners.org)

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**Geriatric Psychiatry Division: Contacts** 

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**Opportunities to Participate in Clinical Research:**

- o **Aniqa Rahman**
  - o arahman@mclean.harvard.edu
  - o 617-855-2511

**Memory Clinic referrals:**

- o **Laurie Albanese**
  - o Albanel@partners.org
  - o 617-855-3267

**Other resources:**

Alzheimer's Association MA/NH:

- o [www.alz.org/manh/](http://www.alz.org/manh/)

Alzheimer's Association TrialMatch

- o [www.alz.org](http://www.alz.org)

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