

MODERN TRENDS IN THE TREATMENT OF DEMENTIA

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Definition

- According to DSM-5, released in 2013, the criteria for dementia (now called major neurocognitive disorder) include the following
 - Evidence from the history and clinical assessment that indicates significant cognitive impairment in at least one of the following cognitive domains:
 - Learning and memory
 - Language
 - Executive function
 - Complex attention
 - Perceptual-motor function
 - Social cognition
- Must be acquired and represent a significant decline from previous level of functioning.
- Must interfere with independence in everyday activities.

Ref: American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), American Psychiatric Association, Arlington, VA 2013.

Agnosia



Imagine not being able to recognize your best friend.

Statistics

- Starting at age 65, the risk of developing dementia doubles every five years.
- By age 85 years and older, between 25 and 50 percent of people will exhibit signs of Alzheimer disease.
- Up to 5.3 million Americans currently have Alzheimer's disease.
- By 2050, the number is expected to more than double due to the aging of the population.
- Alzheimer disease is the sixth leading cause of death in the United States and is the fifth leading cause among persons age 65 and older.

HOW TO HELP STAVE OFF ALZHEIMER'S: WHAT THE EXPERTS SUGGEST.

Keep Fit!

Engage in moderate exercise at least 3 times a week.

Maintain a healthy, balanced diet.

Maintain an active social life.

Enjoy brain challenges like puzzle activities, cards and board games.



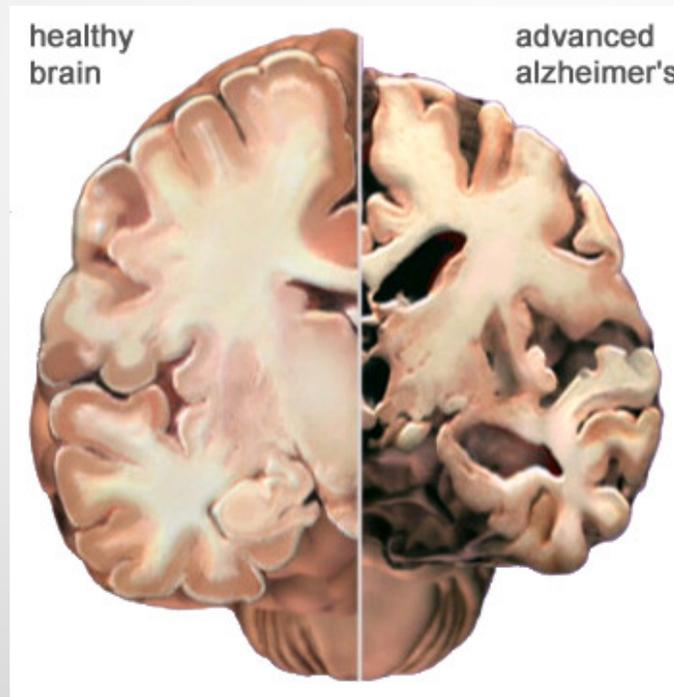
Prevention

- Numerous observational studies on
 - Use of dietary supplements
 - Diet
 - Physical activity
 - Socioeconomic factors
 - Co-morbidities
 - Environmental exposures
 - Cognitive engagement
- No proof that modification of these factors reduces the risk of dementia.

Types of Dementia

- Alzheimer disease (AD) accounts for the majority of cases- 60-80%.
- Vascular dementia
- Lewy body dementia
- Parkinson-related dementia
- Alcoholic dementia
- Fronto-temporal dementia

Brain changes in advanced AD



Ref: <http://thebrainbank.scienceblog.com/2013/03/25>

Clinical course and prognosis

- Dementia is a terminal illness
- Stages of dementia
 - Mild or early stage
 - Moderate
 - Moderately severe
 - Severe

Tools Used To Assess Progression of Dementia

- Folstein's Mini-mental Assessment Scale
 - Mild to moderate
 - Scores 25-30 normal. Less than 10 severe dementia
- Functional Assessment Staging
 - Moderate to severe
 - Scores 1: normal, 7c hospice eligible.
- Karnofsky Performance Scale
 - Performance progress through any terminal illness
 - Scores 100% : normal, decrease by multiples of 10 down to a score of 10% when patient is moribund.
- Global Deterioration Scale
 - Stage 1: normal, Stages 4-7 severe dementia

Ref: Lisa Graham AAFP and ACP Release Guideline on Dementia Treatment. Am Fam Physician
2008 Apr 15; 77(8):1173-1175

Family meeting

Discussion with patient and caregiver on disease progression:

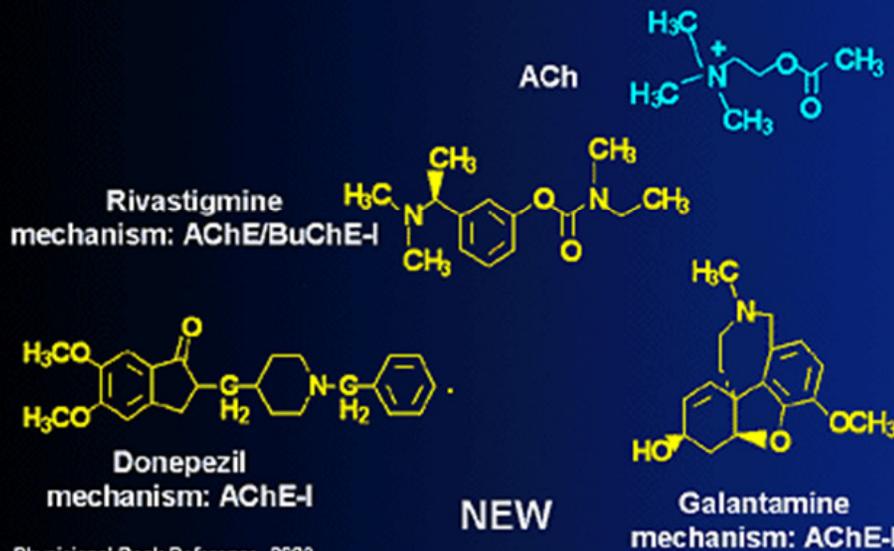
- Early in illness so patient can participate.
- Many matters to be discussed including
 - Medical
 - Social
 - Psychological
 - Ethical
 - Spiritual

Treatment of Dementia

- Main focus
 - Enhance quality of life
 - Maximize functional performance
 - Improve cognition, mood and behavior.
- Types of treatment
 - Pharmacological
 - Non-pharmacological

Current pharmacological treatment

Cholinesterase Inhibitors



Physicians' Desk Reference, 2003.



Pharmacological treatment

Cognitive enhancers

- Acetylcholinesterase inhibitors
 - Donepezil
 - Rivastigmine
 - Galantamine
- NMDA receptor antagonists
 - Memantine

Pharmacological treatment

Behavioral problems are among the main reasons why dementia patients are placed in long term care facilities.

- Agitation with non-acute psychosis
 - Risperidone (FDA warning about cerebrovascular events)
 - Olanzapine (Use with caution in diabetics)
 - Quetiapine (Useful for patients with Parkinsonian symptoms)
 - Ariprazole
- Acute agitation
 - Haloperidol
- Sleep disturbances
 - Melatonin, Trazodone, non-benzodiazepine hypnotics.

Avoid antipsychotics in patients with Lewy body dementia.

Ref: Charles D. Molsinger. Use of atypical antipsychotic drugs in patients with dementia. Am Fam Physician. 2003 Jun 1;67(11): 2335-2341.

Ref: A. deLonghe. Effectiveness of melatonin treatment on circadian rhythm disturbances. Int J Ger Psychiatry 2010; 25: 1201-1208.

Pharmacological treatment

- Agitation with anxiety and irritability
 - Trazodone
 - Buspirone
- Agitation with depression
 - Citalopram
- Agitation with significant aggression (second line treatment)
 - Divalproex
- Sexual aggression, impulse control in men
 - Atypical antipsychotics
 - Divalproex
 - Second line treatment: Estrogen, medroxyprogesterone

Ref: Rueben D et al, Geriatrics at Your Fingertips 2014, 16th edition.

Other agents

- Conflicting evidence about the benefits of
 - Selegiline (a MAO type B inhibitor with minimal anticholinergic effects)
 - Testosterone
 - Ginkgo biloba (neuroprotective agent, anti-oxidant and free radical scavenger)
- No evidence supporting the beneficial effects
 - Vitamin E
 - Estrogen
 - NSAIDs
 - Statins
 - Insulin sensitizers
 - Lecithin
 - Acetyl-L-carntine

Ref: Bradford T. Winslow et al. Treatment of Alzheimer's disease Am Fam Physician 2011 Jun 15; 83(12): 1403-1412.

Monitoring therapy

- Alzheimer's Disease Assessment Scale of cognition (ADAS-Cog) and the Clinician Interview-Based Impression of Change Scale plus Caregiver Input (CIBICS-CI) are the most commonly used instruments to establish effectiveness of AD medications in clinical trials.
- Lengthy and cumbersome.
- MMSE: familiar to most physicians but non specific.
- No subspecialty group guidelines give concrete recommendations regarding how monitoring should be done or which tools should be used.
- The Alzheimer's Association suggests post-diagnostic monitoring every 6 months or any time there is a behavioral change or sudden decline in function.

Ref: Jaqueline Raetz. Monitoring therapy for patients with Alzheimer's disease.
Am Fam Physician 2007 Jun 1; 75(11): 1703-1704

When should medications be discontinued?

- Patient does not adhere to treatment.
- Deterioration continues.
- Patient develops serious co-morbid disease or is terminally ill.
- Patient or caregiver chooses to discontinue treatment.
- A brief medication free trial may be used to assess whether a medication is still providing a benefit.

Non pharmacological treatment

- Familiar surroundings
- Daily routines
- Environmental modifications
 - Clocks
 - Calendars
 - To do lists
 - Pictures of a toilet on the bathroom door
 - Pictures of food on the dining room door
 - Stop signs on the entrance doors
- Environmental safety

Ref: Abi V. Rayner. Behavioral Disorders of dementia: Recognition and treatment.
Am Fam Physician 2006 Feb 15; 73(4): 647-652.

Non pharmacological treatment

- Cognitive rehabilitation
 - Reality orientation
 - Memory retraining
 - Cognitive training
- Problem: inability to learn new skills
- Solution: provide support to accommodate lost skills.

Non pharmacological treatment

- Stimulation oriented treatment
 - Art
 - Music
 - Dance
 - Pet therapy
- Emotion oriented psychotherapy
 - Pleasant events
 - Reminiscent therapy
- Emotional connection with partner: expressions of feelings, closeness, touch, massage and cuddling.

These are especially useful for patients with behavioral problems.

Special care units

- Only about 13% of all long term facilities have dementia special care units.
- Patients with similar needs are placed together.
- Staff is specially trained to deal with dementia patients and are thus more able to give quality supportive care to the patient.
- Goals of a successful dementia unit include
 - Maximize safety and support
 - Facilitate social opportunities
 - Support of functional abilities
 - Provide opportunity for control and privacy
 - Adjust the amount of stimulation
 - Maintain self identity
 - Maximize awareness and orientation

Ref: Sue Lanza. www.elderlink.com/Alzheimers-and-Dementia/do-special-care-units-work-dementia-care.htm

Dementia Village Weesp, The Netherlands

- In 2009, Hogeweyk, a neighborhood for dementia patients in the Dutch town of Weesp, near Amsterdam, Holland.
- Wandering is one of the symptoms of dementia. Residents can move around freely in the village but they cannot leave.
- This sort of village environment allows patients with dementia to live with dignity in safe environs.
- Observational studies indicate that patients are more active and require less medication.
- Another dementia village is in the planning stages in Wiedlisbach, canton Bern, Switzerland.
- Will we have one in USA any time soon?

Supermarket, Dementia village,



Housing: Dementia Village, Weesp

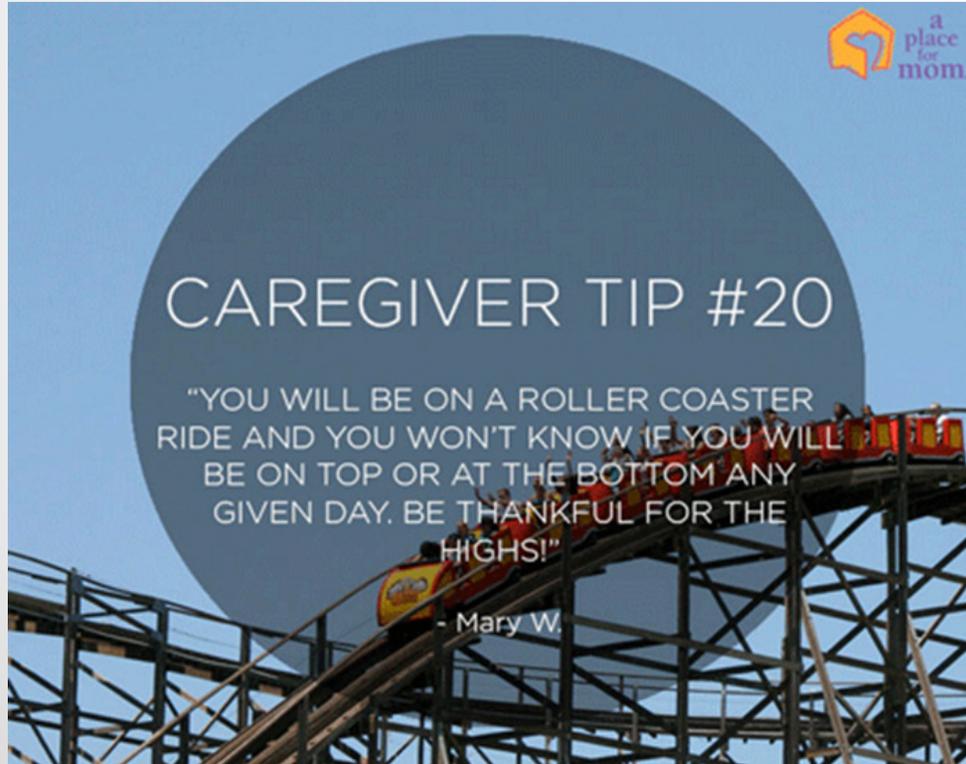




CAREGIVER TIP #20

"YOU WILL BE ON A ROLLER COASTER RIDE AND YOU WON'T KNOW IF YOU WILL BE ON TOP OR AT THE BOTTOM ANY GIVEN DAY. BE THANKFUL FOR THE HIGHS!"

- Mary W.



Caregiver Support

- Caregiver stress.
- Isolation.
- Anticipatory grief.
- Respite care and support groups.
- Local agency on aging.
- Alzheimer's Association.
- Physician's role.

New modalities

- No new drug has been approved for the treatment of AD for more than 10 years.
- Old drugs aimed at treating dementia signs and symptoms.
- New modalities aim at treating the root cause of dementia in the brain cells.

Ref: Pharmacological recommendations for the symptomatic treatment of dementia: the Canadian Consensus Conference on the Diagnosis and Treatment of Dementia 2012.

Beta-amyloid

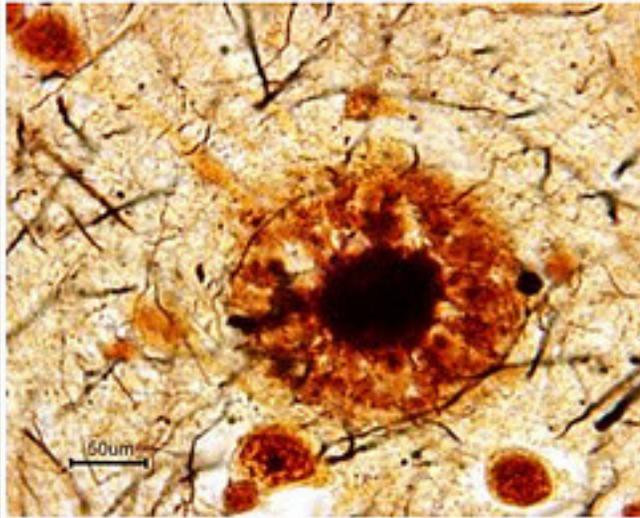
- Chief component of plaques
 - A hallmark of AD
 - Clipped off from parent compound amyloid precursor protein (APP) by 2 enzymes
 - Beta-secretase
 - Gamma-secretase
 - Two humanized monoclonal antibodies, bapineuzumab and solanezumab, directed against the N terminus and mid-region of Beta-amyloid, respectively are being tested in phase III trials in patients with mild to moderate AD. Aim: To confirm beneficial cognitive effects shown in previous studies.

Ref:1. www.alz.org/research/science/alzheimers_treatment_horizon.asp

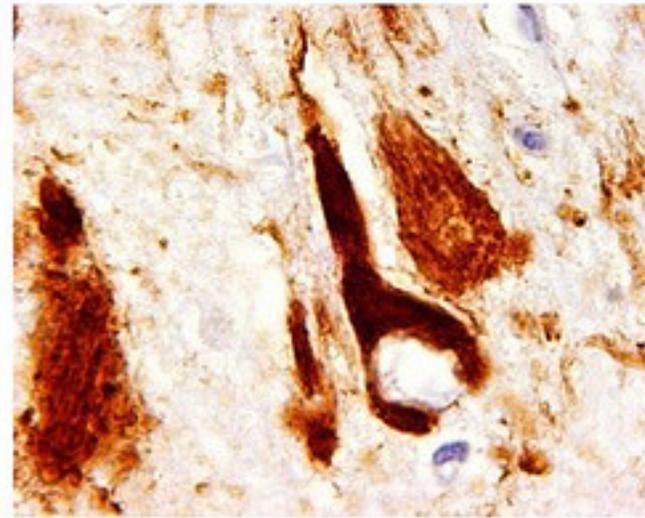
2. Expert Opin Biol Ther 2014 Jun 30: 1-12.

Beta-amyloid plaques & Tau tangles

Plaques



Neurofibrillary Tangles



Immunotherapy

- Both active and passive vaccinations with beta-amyloid have been tested in clinical trials.
- Tau based therapies have so far only been tested in mice.
- Beta-amyloid immunotherapy may delay the onset of dementia.
- Phosphorylated tau immunotherapy might delay the progression of AD.

Ref: Lambracht-Washington D. Anti-amyloid beta to tau based immunization: Developments in immunotherapy for Alzheimer disease. *Immunotargets Ther.* 2013 August 1;2013(2): 105-114.

Inflammation

- Excess pro-inflammatory mediators, some of which may cross the blood-brain barrier may trigger neurodegeneration.
- In a recent study in mice with AD, a heptapeptide isolated from the Ph.D-C7 library by phage display significantly improved the spatial memory and reduced the amyloid plaque burden.

Ref: Zhou W. W. et al. Decreasing oxidative stress and neuroinflammation with a multifunctional peptide rescues memory deficits in mice with Alzheimer disease. Free Radic Biol Med 2014 Jun 21 pii; S0891-5849(14)00265

Insulin Resistance

- Insulin receptors are distributed throughout the brain.
- Modulates neurotransmitter channel activity, cholesterol synthesis, mitochondrial function and phosphorylation of tau protein.
- Disruption of insulin action in the brain leads to impairment of neuronal function and synaptogenesis.
- Thus, alteration in insulin action can contribute to the development of neurodegenerative diseases like AD.

Ref: Kleinridders A et al. Insulin action in brain regulates systemic metabolism and brain function.
Diabetes 2014 Jul 63(7): 2232-43.

Caprylidene (Axona)

- Medical food marketed since 2009 to assist with the dietary management of AD.
- Main ingredient caprylic triglyceride – fractionated coconut oil, a medium chain triglyceride.
- MOA:
 - Caprylic acid is broken down to ketones when digested.
 - Alternative energy source for the brain.
 - In AD the brain's ability to utilize its normal energy source (glucose) is impaired.
- Caprylidene is not approved as a drug to treat AD by FDA.
- No evidence to substantiate its efficacy to treat AD.
- Accera Inc. the manufacturer of Axona has paid for and conducted the only clinical trial published in an open access journal.

In the pipeline

- Electroconvulsive therapy (ECT).
 - Venue: Mclean Hospital in Belmont, Massachusetts, USA
 - Aim: To find out whether patients receiving ECT or standard care differ in reduction of agitation/aggression severity and changes in cognition pre- and post-treatment.
- Far infrared Radiation
 - Venue: The Centre for Incurable Diseases Toronto, Canada
 - Aim: To determine the therapeutic effects of infrared radiation on dementia.
- Tolcapone
 - Venue: Columbia University, NY, USA
 - Aim: To test the effects of Tolcapone (This increases the amount of dopamine in the brain.) in patients with fronto-temporal dementia.

Yarumal, Columbia

- Earlier I mentioned Weesp, the Dutch AD village.
- That one was artificially created.
- In Yarumal, Antioquia region of Columbia over 5000 members of 25 families have a mutation in the presenilin gene-1 on chromosome 14
 - “Piasa variation” of AD= Autosomal-Dominant AD (ADAD) = La bobera = “The stupidity”
 - Inbred communities, all descendants of a single Basque who settled in the area in the 18th century
 - Develop AD much earlier – in the 5th decade
 - Identical brain lesions to that seen in mainstream AD
- Alzheimer’s Prevention Initiative (API), an international public-private consortium has been established to conduct research on these families.
 - First clinical studies being done with anti-amyloid therapies.
 - Target: Family members who are known to have the ADAD gene but have not yet experienced symptoms.
 - Aim: To delay or prevent AD in these members.

Ref: Michael Jacobs. Yarumal, Columbia: the largest population of Alzheimer’s sufferers.
www.telegraph.co.uk/health/9617320/Yarumal-Columbia

Yarumal



Yarumal



Summary

- Dementia is a very stressful illness for the patient, the caregiver, and caring family members so continuing research needs to be done on prevention, treatment and a possible cure.
- Modern trends in treatment include
 - Dementia villages
 - Vaccines
 - Research on ECT, infrared radiation
 - Food supplement: Axona
 - Drugs that modify the disease process
- It is important to do advanced care planning while the patient still has decision making capacity.
- The multidisciplinary hospice team can help to make the end of life issues for these patients and their caregivers much more bearable but hospice is underutilized and often utilized too late.
- Caregivers should be encouraged to use support groups and try to maintain a life outside of caring for the dying patient.
- The physician has a pivotal role not just in the medical management of dementia patients but we must also be cognizant of the other domains: functional, psychological, ethical, and spiritual.



Questions?