Outpatient Geriatric Psychiatry Pharmacology

Steven Huege, MD, MS.Ed
Clinical Professor
Division of Geriatric Psychiatry
UCSD School of Medicine

UC San Diego
School of Medicine

Outline

- Introduction
- Aging
- Medication classes
- Supplements
- Agitation
- Conclusion

What do we (geriatrics) treat?

What is different?

- Changes associated with aging
  - Delayed gastric emptying
  - Decrease renal clearance, GFR
  - Changes in fat/water ratio
  - Reduced hepatic blood flow
  - Lower muscle mass

Complexity…

- Seniors:
  - More medical conditions
  - More medications- average is 15!
  - More potential for interactions

Important to look at *all* meds

- Non-psychiatric meds can have psychotropic effects
  - Antihypertensives
  - Antihistamines
  - Herbal products
  - Endocrine meds: thyroid, steroids
  - Pain meds

Antidepressants

- SSRI's: sertraline, citalopram, escitalopram
- SNRI's: venlafaxine, duloxetine
- TCA: nortriptyline
- Others: buproprion, mirtazepine

Anxiolytics

- Benzos: with caution- associated w/ increased risk of dementia
- Gabapentin
- Buspirone
- Trazodone??

Antipsychotics

- Atypicals preferable: olanzepine, risperidone,
- Haldol, perphenazine

Antipsychotics

- Often can be helpful in treatment of agitation
- Use carefully
- CATIE-AD: “Adverse effects offset advantages”
- Black Box Warning
- Have a place in treatment- must weigh risk of untreated agitation

Risperidone Discontinuation

- Devanand, et.al. Looked at pts with AD who had a positive response to risperidone
- Subjects who were taken off risperidone showed higher risk of relapse of agitation and/or psychosis than those who cont treatment with risperidone

Mood Stabilizers

- Valproate, carbamazepine- LFT's CBC, ammonia
- Li- thyroid, renal/lytes

Cholinesterase Inhibitors

ChE Inhibitor	Year Introduced	AChE Inhibition	BChE Inhibition
Tacrine *No longer used*	1993	+	+
Donepezil	1996	+	-
Rivastigmine	2000	+	+
Galantamine	2001	+	-

Targets for Disease Modifying Therapies

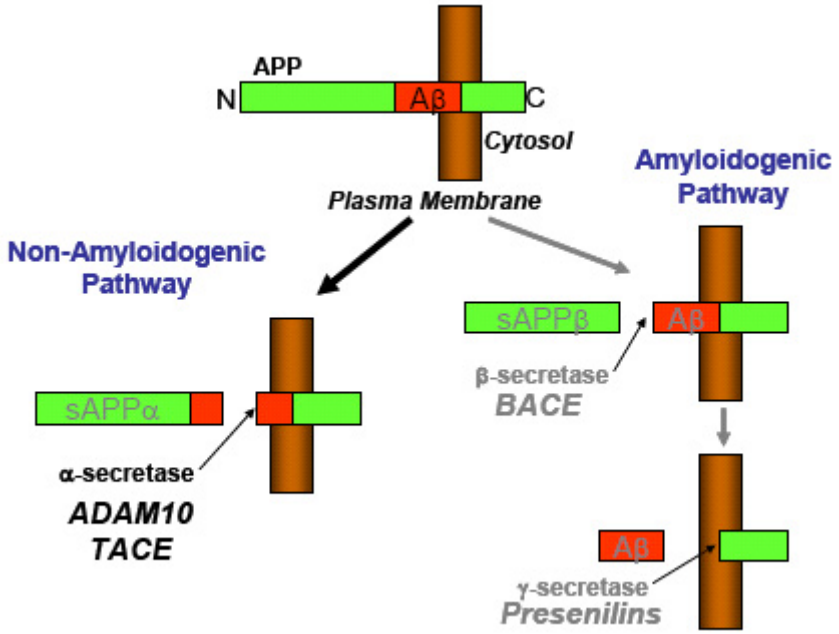
- Amyloid
- Immunization
- Tau
- Oxidative stress

AD Pathophysiology

- Familial Alzheimer's (presenilin genes)
  - Chromosomes 1, 14, and 21
- Down's Syndrome (APP)
  - Chromosome 21
- Apolipoprotein E
  - Chromosome 19
- Neurofibrillary tangles (phosphorylated tau)
  - Chromosome 17

Amyloid Pathway

www_fbs_leeds_ac_uk



Decrease Amyloid Production

- Inhibition of two proteins involved in generation of Aβ peptides
  - β secretase (BACE)
  - γ secretase (presenilin)

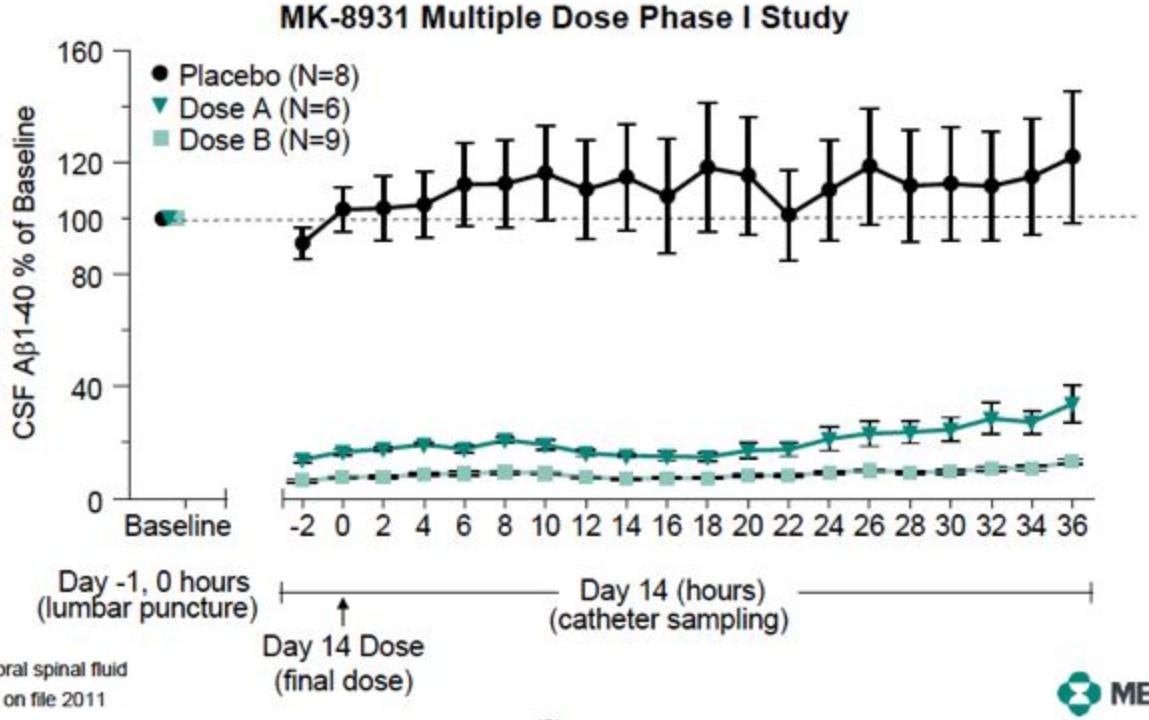
Evidence from transgenic/knock-out mice that inhibition of these two proteins leads to decreased/absent Aβ production

MK8931

- BACE inhibitor produced by MERCK, phase 2 clinical trials
- Lowered Aβ in csf
- On-going separate Phase 3 clinical trials in Amnestic MCI (Prodromal AD) and Early AD subjects

MK-8931 Robustly Suppresses Aβ Levels in CSF

- CSF Aβ peptides were lowered >90% in once-daily oral, single, and multiple dose healthy volunteer studies without dose limiting side effects being observed



CSF=Cerebral spinal fluid

Merck data on file 2011

MERCK

LY450139

- Clinical trial of oral γ secretase inhibitor
- Phase III trial discontinued (August 2010) because patients on active drug worsened at a greater rate than those on placebo
- Also pts on active drug greater incidence of skin cancer compared to placebo

Increase Non-amyloidogenic pathways

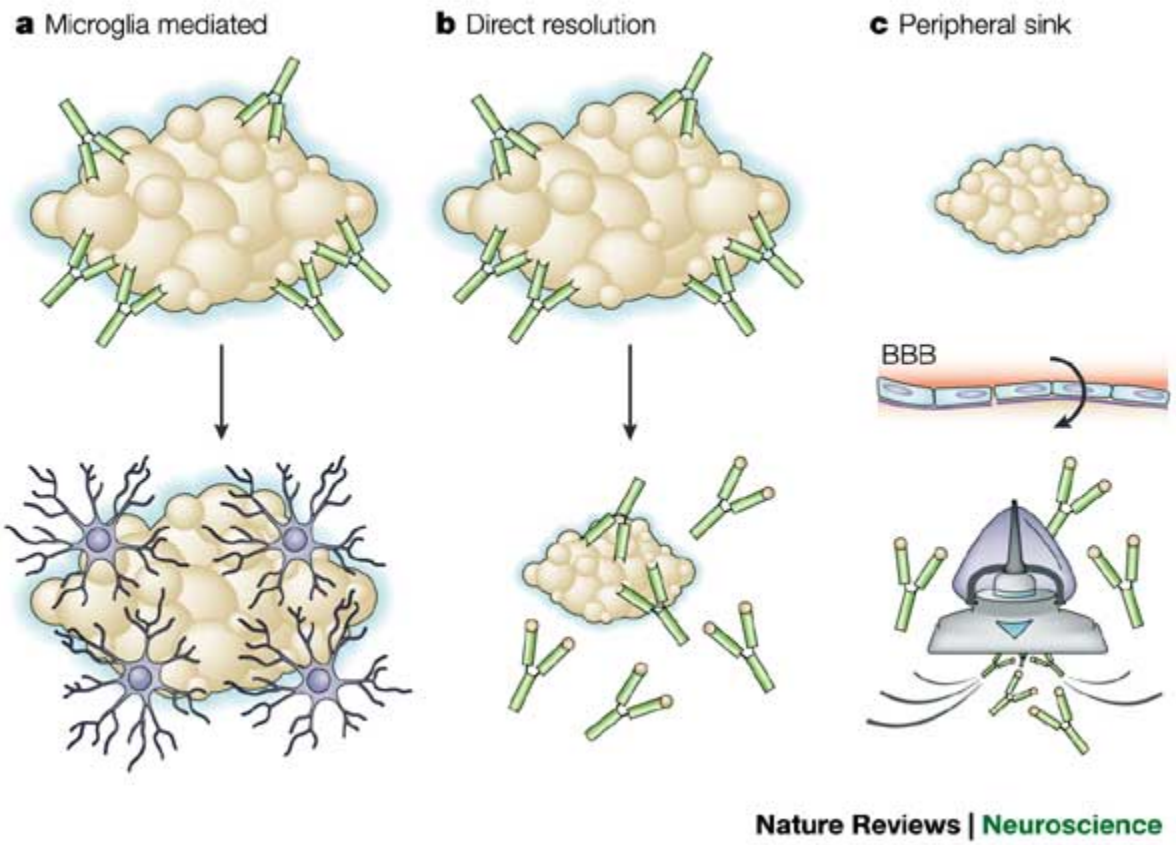
- Stimulate cleavage of APP by α-secretase (ADAM-10)
- Evidence that over-expression of α-secretase reduces amyloid plaque formation and alleviates deficits in spatial learning in animal studies

Immunization

- Schenk and colleagues immunized PDAPP transgenic mice prior to their development of amyloid plaque deposits with aggregated $A\beta_{1-42}$ which led to a decrease in amyloid pathology and neuritic pathology
- Similar results with clearing of amyloid plaques occurred in older mice who were immunized with Aβ
- Direct administration of anti-Aβ -antibodies also produced a reduction in amyloid pathology in transgenic mice- No need to rely on direct immune response (passive immunization)

Mechanisms for Immunization

www.nature.com/.../v5/n9/images/nrn1495-f2.jpg



Immunization (Active) Trial

- Aβ vaccine AN 1792- synthetic Aβ peptide + QS-21 (T-helper adjuvant)
- 2002 Phase II trial halted after 18 cases (6%) subjects developed meningoencephalitis
- Evidence that subjects who had high antibody titers showed greater brain volume decrease (suggesting clearance of amyloid plagues) and decelerated cognitive and behavioral decline

Gilman et al. Neurology 2005, Fox NC et al. Neurology 2005

Immunization (Passive) Trials

- Bapineuzumab- monoclonal antibody for Aβ
  - Aug 2012: Studies halted due to failure to achieve significant improvement on measures of cognition and function
- Solanezumab- monoclonal antibody for Aβ
  - Also failed to reach cognitive and functional endpoints, but did show a *slowing* of cognition
- IVIG Trial- Negative

A4 Study

Anti-Amyloid Treatment in Asymptomatic AD

- Trial of solanezumab vs placebo in clinically asymptomatic adults age >65 with “positive” amyloid imaging scans
- Florbetapir – amyloid imaging compound being used
- Three yr trial

DIAN

Dominantly Inherited Alzheimer Network

- Clinical trial involving subjects with known or possible presence of autosomal dominant genes for causing AD (APP, PSEN 1,2)
- Trial of either Solenuzemab or Gantenerumab vs placebo

AADvac1

- Tau peptide (DC8E8) vaccine designed to stimulate an active immune response against pathological form of tau
- Showed removal of tau and improvement in transgenic mice
- Passed Phase I clinical trials, 30 pts- no cases of meningoencephalitis
- Phase 2 clinical trial- on-going scheduled for completion 2019

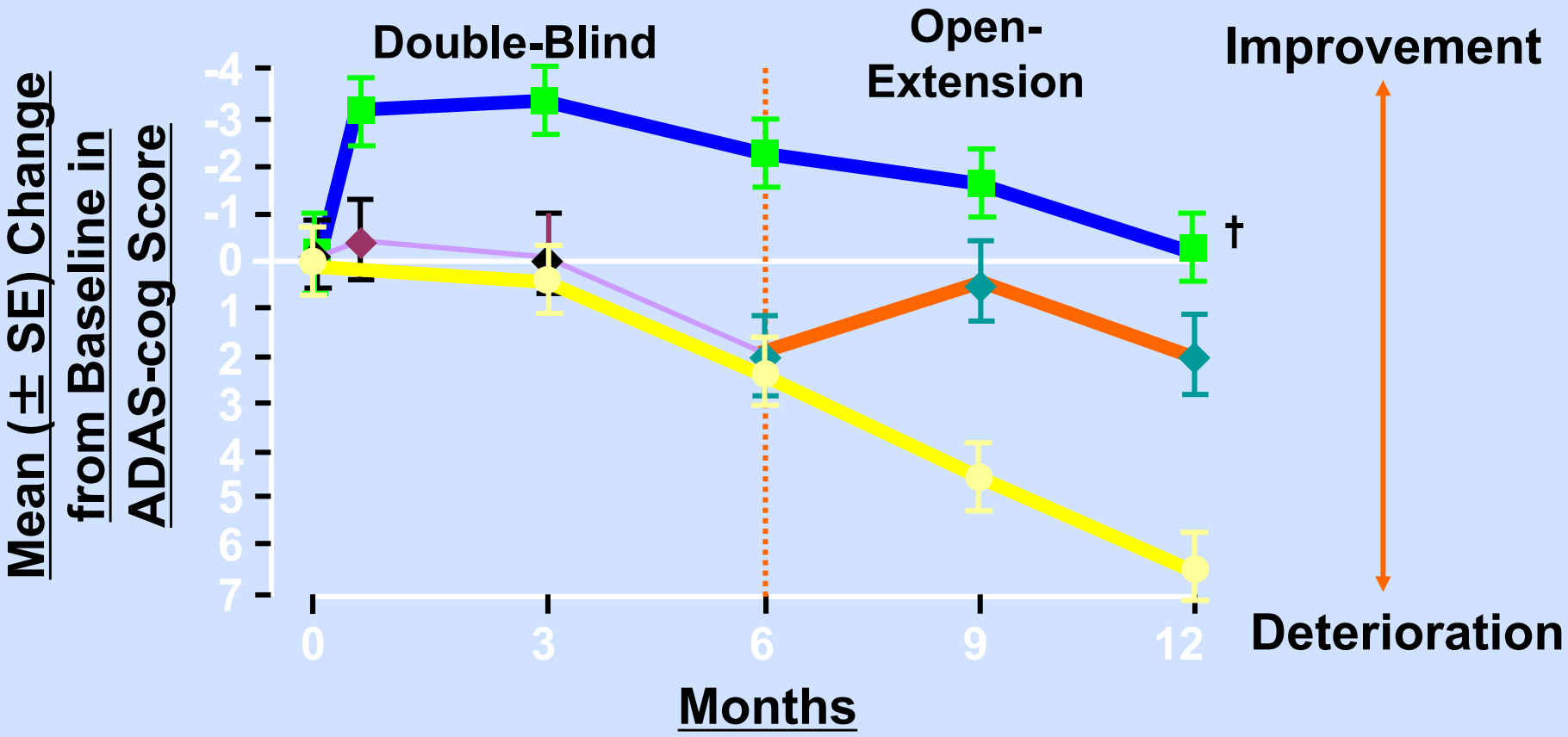
ChE- Inhibitors

- Need minimum of two well-designed clinically relevant trials (pivotal trials)
- Assessment of efficacy in AD trials, regulators require at least statistically significant effects on 3 endpoints:
  - Cognition- ADAS-Cog
  - Global functioning- CIBIC-Plus
  - Activities of daily life

Efficacy of ChEI

- Modest benefit- stabilize cognitive decline for about 6 mths
- Other benefits: fewer behavioral changes, less burden to care-givers, and delayed nursing home placement- suggested by some secondary measures in CT's but these were not randomized

Effect of Galantamine on Cognition: ADAS-Cog*



*ADAS-Cog = Alzheimer's Disease Assessment Scale-Cognitive Subscale; †p<0.05 vs. placebo/ Galantamine and not statistically different from baseline; Raskind MA et al. Neurology. 2000;54:2261-2268

Glutamate and AD

- Glutamate is principal excitatory neurotransmitter in cortical and hippocampal neurons
- Excessive activation of NMDA receptors by glutamate increases vulnerability of CNS neurons leading to neuronal degeneration
- Such neuronal degeneration may be responsible for cell death and ultimately clinical symptoms of AD

Memantine

- Low to moderate affinity NMDA receptor antagonist
- Approved in 2003
- Indicated for advanced stages of AD

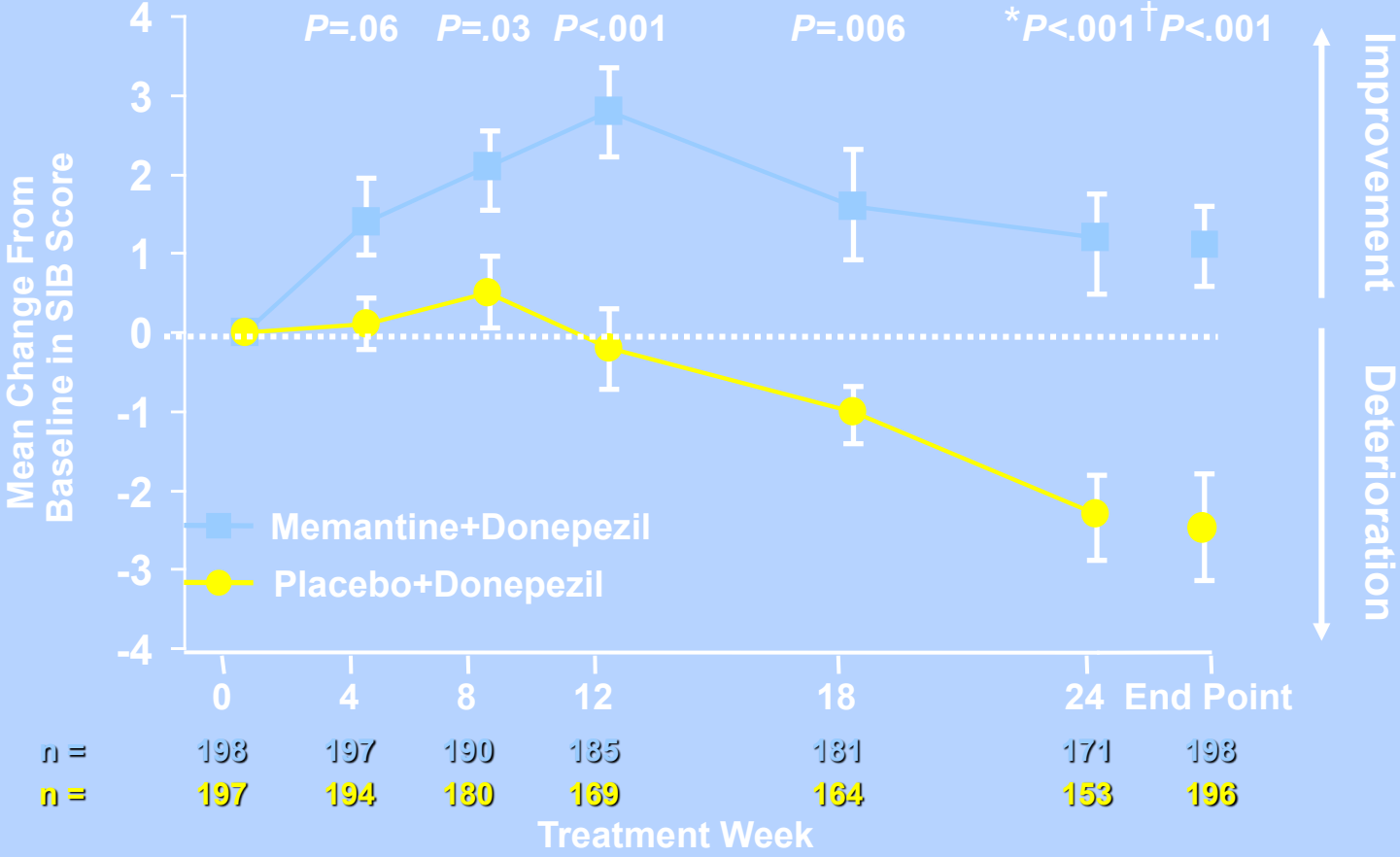
Memantine Efficacy

- Cochrane review:
- Small beneficial effect at 6 mths. in moderate to severe AD on cognition, ADL's, and behavior
- McShane R, et. al, Memantine for Dementia Cochrane Database Syst Rev 2006
- Study showed significant reduction in nursing time, extended time to institutionalization, and maintenance of autonomy relative to placebo
- Heinen-Kammerer et. al. Clin Drug Invest. 2006
- Generally well tolerated in studies: dizziness, headache, constipation, somnolence > placebo

Memantine + Donepezil

- RCT by Tariot et. al. 2004
- Patients on stable doses of donepezil comparison of donepezil + memantine vs donepezil + placebo
- Demonstrated significantly better outcomes on measures of cognition, ADL's, global outcome, and behavior in donepezil + memantine subjects

Memantine + Donepezil Study: Cognition (SIB)



*OC analysis. †LOCF analysis.
Adapted from Tariot P, et al. *JAMA*. 2004;291:317-324.

Nuedexta

- Dextromethorphan/quinidine
- Quinidine increases blood levels of dextromethorphan
- Only ”approved” for treatment of pseudobulbar affect
- Used “off label” for agitation

Pimavanserin

- Combination of inverse agonist and antagonist activity at the serotonin 2A receptors (5-HT_{2A}) and, to a lesser extent, at the 5-HT_{2C} receptors
- Treatment of psychosis related to Parkinson's Dis

Supplements

Nutraceutical

- Term first used by Stephen DeFelice, M.D.- CEO of Foundation for Innovation in Medicine
- Combination of '*nutrition*' and '*pharmaceutical*'
- 'A nutraceutical is any substance that is a food or a part of a food and provides medical or health benefits, including the prevention and treatment of disease'

http://www.ana-jana.org/nut_info_details.cfm?NutInfoID=4

Health Canada - Definition

- A *nutraceutica*l is a product isolated or purified from foods that is generally sold in medicinal forms not usually associated with food. A nutraceutical is demonstrated to have a physiological benefit or provide protection against chronic disease.

http://www.hc-sc.gc.ca/fn-an/label-etiquet/claims-reclam/nutra-funct_foods-nutra-fonct_aliment-eng.php

FDA

- Nutraceutical has no specific regulatory meaning in US
- *Dietary supplement*
- ‘A product taken by mouth that contains a "dietary ingredient" intended to supplement the diet.’
- Regulated by Dietary Supplement Health and Education Act (DSHEA) of 1994

DSHEA 1994

- Dietary ingredient: one or any combination of the following substances:
  - Vitamin
  - Mineral
  - Herb or other botanical
  - Amino acid
  - A dietary substance for use by man to supplement the diet by increasing the total dietary intake (e.g., enzymes or tissues from organs or glands)
  - Concentrate, metabolite, constituent or extract

DSHEA

- DS do not need FDA approval prior to marketing
- Firms are responsible for safety of products and that claims are not false or misleading
- No requirement to provide FDA with evidence used to establish safety or efficacy
- ‘New dietary ingredients’ not marketed prior to October 15, 1994 – most demonstrate product is “reasonably expected to be safe for use in a dietary supplement.”
- FDA must show supplement is unsafe prior to ordering restriction or removal from market
- Manufacturer cannot make claim that DS is a treatment, prevention, or cure for a specific disease or condition

http://www.fda.gov/Food/DietarySupplements/ConsumerInformation/ucm110417.htm#what

Spending on Nutraceuticals

- US retail sales in 2008 in $ billions:
  - Functional/Fortified Foods & Beverages : $40.5
  - Organic Foods/Beverages: $23.6
  - Vitamins, Minerals, Herbal & Dietary Supplements: $23.3
  - Natural Foods/Beverages: $14.6

http://www.nutraceuticalsworld.com/news/2009/05/21/Health%20%2526%20Wellness%20Industry%20Sales%20Top%20%24112%20Billion

Use of Alternative Medicines by Seniors

- Age > 65:
- 30% any modality of alternative medicine
- 8% use herbal remedies
- 5% use high dose vitamins
- 6% take both herbs and prescription medications
- 57% did not mention use of alternative medicines to their doctor

Foster, D. Alternative Medicine use in Older Americans, JAGS 48(12) 2000.

Use of Alternative Medicines by Alzheimer's Patients

- Survey of Caregivers of AD pts.
- 55% tried at least one alternative therapy to improve memory
- 27% tried 3 or more
- Therapies used
  - Vitamins 84%
  - Health foods 27%
  - Herbal medicines 11%
  - "Smart pills" 9%
  - Home remedies 7%

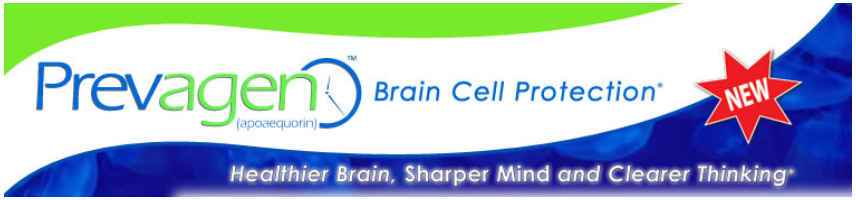
Coleman, LM Use of unproven therapies by people with Alzheimer's disease. J. Am Geritr Soc 43:747-750 1995

What's out there??

(What are patients buying?)

Too good to be true?

Fountain of Youth or False Promises ?



What does evidence say?

- Just because something is “natural” does not necessarily mean that it works or does not work
- Like any other intervention, we must look at the science

Ginkgo biloba

- Ginkgo tree (maidenhair tree) native to China
- Extracts have been used for thousands of years in Chinese medicine – circulatory problems, vertigo, cognitive enhancement
- Introduced in Germany 1965
- Sales of ginkgo products $ 249 million - US

Ginkgo Biloba

- Ginkgo formulation used in most products is an extract EGb 761 – 24% w/w flavone glycosides and 6% w/w terpene lactones
- Mechanism of action: antioxidant, enhancement of cerebral blood flow, anti-platelet aggregation, anti-amyloid effects?

Ginkgo for cognition/dementia

- 1997 Study: 52 wk, RPC, uncomplicated AD significant benefit – unlikely clinically meaningful
- 2005 Study – 6 mth RPC, AD, no benefit
- DeKosky 2008– G. biloba 120 mg BID, not effective in reducing incidence rate of AD in elderly with MCI or normal cognition
- Cochrane Review 2009: “There is no convincing evidence that G. biloba is efficacious for dementia and cognitive impairment”
- In one study: Higher rate of stroke and TIA amongst GBE group compared to placebo

Acetyl-L-Carnitine

- Most common short-chain acetyl carnitine ester of L-carnitine
- Plays important role in energy/lipid metabolism and membrane composition
- May also regulate enzyme activity

ALC and dementia

- 12 mth – RDBPC trial 431 pts with probable AD – measures CDR and ADAS-Cog, 3 grams daily, No benefit of slowing progression of AD
- 12 mth trial in Early on-set AD also showed no benefit
- Cochrane review of ALC in dementia – 16 studies- no benefit for dementia in measures of clinical severity, ADL's, cognition

Huperzine A

- Alkaloid isolated from Chinese herb *Huperzia serrata*
- Used for centuries in Chinese medicine to treat fever, swelling and blood disorders

Huperzine A

- Potent, highly selective, reversible cholinesterase inhibitor
- Rapid absorption, widely distributed throughout the body, good blood-brain barrier penetration
- Other action: antioxidant, alteration of amyloid production?
- Approved for treatment of AD in China 1994

Efficacy of Huperzine

- 2009 Meta- analysis by Wang MMSE primary cognitive measure. 11 Articles, duration of studies 8 – 24 weeks, 2 double blinded controlled studies
- Demonstrated Hup A improved MMSE score of AD patients by mean difference of change 3.5 ($p < 0.05$)
- No published trials outside of China
- Phase II clinical trial in US, completed 2007, P. Aisen – PI. Awaiting results

Phosphatidylserine

- One of five phospholipids that contribute to structure of cell membranes
- Synthesis requires substantial energy expenditure
- Most PS comes from dietary sources
- Age related loss of dendritic spines – ameliorated by PS in rats

Phosphatidyserine

- Supplements derived from either soy or bovine cerebral cortex – differ in composition
- Clinical trials for memory/dementia used BC-PS – halted due to worries about transmissible spongiform encephalopathy
- Two trials of BC-PS in AD failed to show evidence of cognitive improvement
- No soy derived PS trials are underway

Omega 3 Fatty Acids

- n-3 polyunsaturated fatty acids – derived from fatty fish – salmon, tuna, trout
- Eicosapentaenoic acid (EPA)
- Docosahexanoic acid (DHA)

n-3 PUFA

- DHA 8% dry weight of brain
- EPA not detected in the brain
- EPA may influence metabolism in the brain via ketogenesis
- Epidemiological evidence that high intake of fish – DHA – lower incidence of AD, except for APOE 4 +

Mechanisms of action for DHA and Alzheimer's

- Rat studies – DHA lowered brain cholesterol
- DHA decreases inflammatory marker – including COX-2 mRNA
- DHA fed mice had lowered plaque burdens
- DHA also reduced somatodendritc accumulation of tau in 3xTg-AD mice
- May reduce γ-secretase activity

n-3 PUFA and Alzheimer's

- OmegAD study: RDBPC trial, 174 pts, 6 mths, DHA/EPA vs. placebo: ADAS-Cog, MMSE end points, PUFA did not delay rate of cognitive decline in mild-moderate AD. Significant benefit for pts w/ MMSE >27
- 2 other studies:
  - EPA: no effect on cognitive decline in AD (20 pts)
  - AA/EPA: no effect on memory or attention in AD (8 pts)
- Clinical trial: DHA vs. placebo, probable AD, MMSE 14-26, 18 mth RDBPC, awaiting results

Curcumin

(diferulomethane)

- Phenolic yellow curry pigment derived from tumeric
- Use in Ayurvedic medicine for GI disorders, “blood purifier”

Mechanisms of Action of Curcumin in Alzheimer's

- Anti-inflammatory / Anti-oxidant
- Tg2576 mice given curcumin showed reductions in soluble Aβ and decreased amyloid plaque burden
- Interactions with APOE to lower cholesterol

Curcumin and AD

- Ringman, et. al. 24 week, RDBPC study of curcumin in mild – moderate AD, 36 patients, placebo, curcumin 2 or 4 gm, no evidence of benefit on cognitive measures, MMSE, ADAS-Cog, NPI, ADCS-ADL, or biomarker (CSF)
- Efficacy of curcumin may be influenced by poor absorption and low bioavailability
- Efforts to increase bioavailability of curcumin preparations

Axona (caprylidene)

- Newly approved medical food for treatment of mild – moderate Alzheimer's Dementia

Medical food - definition

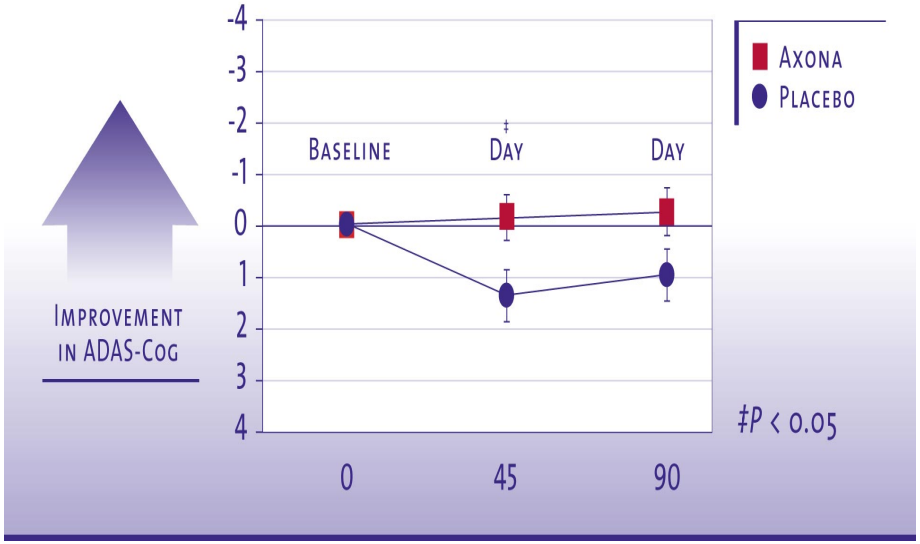
- A medical food was originally defined by Congress as part of the Orphan Drug Amendments of 1988 as “a food which is formulated to be consumed or administered enterally (or orally) under the supervision of a physician, and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation.”

Caprylidene

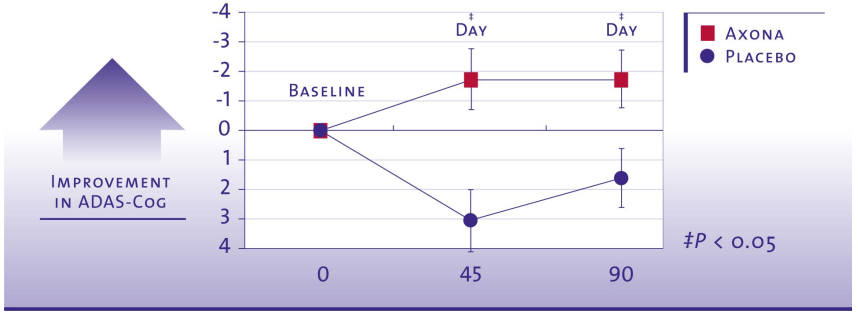
- Proprietary formulation of >95% pure semi synthetic caprylic triglyceride
- Treatment based on premise that glucose hypo-metabolism is a key factor in AD and is thus an appropriate therapeutic target
- Ketone bodies can serve as a substitute for glucose in brain metabolism
- Transformed via gut and liver enzymes into ketone bodies

Efficacy

Significant improvements in ADAS-Cog among all patients with Alzheimer's disease



Significant improvements in ADAS-Cog† for ApoE4(–) patients



Precautions

- Caution in use with pts predisposed to ketoacidosis – alcoholics and diabetics
- Elevation of BUN, creatinine, triglyceride levels
- Exacerbation of underlying GI inflammatory conditions

Axona product insert: http://www.about-axona.com/professionals1.html

Concept of Agitation

- Set of behaviors that cause a disruption in the environment and/or patient care; that may potentially lead to physical or emotional injury of staff, patients, or peers.

Categories

- Verbal Agitation
- Physical Agitation

Verbal Agitation

- Yelling, screaming
- Questioning of staff or demands for attention that becomes intrusive or excessive and impedes pt care
- Use of offensive/inappropriate language

Physical Agitation

- Hitting, biting, attacking of others
- Removal of indwelling medical devices
- Intrusion into personal space of others
- Pacing
- Causing bodily injury to self or others
- Disrobing in public/inappropriate places
- Aggressive or non-consensual sexual activity
- Destruction of property

Assessment of Agitation

- Collaborative effort between staff and physician
- Importance of gathering information

Questions- Behavior

Questions- Behavior

- What happened?
  - Describe behaviors that occurred
  - Who was involved (pt, peers, staff)
  - Assess for any life threatening/serious injury to pt, staff, or others
  - What interventions have been taken thus far- Medication, Behavioral interventions, etc.
  - Context of behavior

Questions- Patient

Questions- Patient

- Who is pt ? – Hx: medical, psychiatric
- Has this ever happened before?
- How does this compare to pt’s usual behavior?
- What is pt like right now- Confused, Agitated, Calm

ABC's of Agitation

- Antecedent – What precipitated or caused the behavior?
- Behavior – What is the behavior?
- Consequence – What is consequence of the behavior?

Differential Diagnosis of Agitation

- Medical
  - Delirium
  - Substance Intoxication
  - Substance Withdrawal
  - Medication Side-effects
- Psychiatric
  - Dementia
  - Psychotic D/o
  - Mood D/o
  - Anxiety D/o
  - Personality D/o

Delirium

- Important to consider
- Sign of an underlying and possibly life threatening illness

Delirium- Signs

- Disturbed/Fluctuating Consciousness
- Inability to sustain attention
- Perceptual disturbances
- Disorientation
- May have periods of hyper or hypoactivity
- Disturbed sleep patterns
- Acute onset, change from usual behavior

Substance withdrawal

- ETOH
  - Symptoms appear 6-12 hrs after last drink
  - Tremulousness
  - Confusion
  - Tachycardia/HTN
  - Nausea/Vomiting
  - Seizures
  - Hallucinations
- Sedative Hypnotic

  (Benzos, Barbiturates)

  -Short acting- Alprazolam

  -On high doses

  -Similar S/S to ETOH

Medication Side-effects

- Anticholinergic meds
- Sedatives
- Opiates
- Steroids
- Parkinson’s meds
- Polypharmacy
- Antipsychotics

Dementia

- Decline from previous level of functioning
- Interfere with activities/work
- Cognitive impairment: Hx, Testing
- Cognitive/Behavioral impairment:
  - Memory
  - Reasoning/judgment
  - Visuospatial
  - Language
  - Personality changes

Psychotic Disorders

- Schizophrenia, Schizoaffective D/o, Delusional D/o
- Presence of:
  - Delusions, Hallucinations, Disorganized TP
  - Hx of psychotic d/o

Mood Disorders

- Major Depression
  - Low mood
  - Anhedonia
  - Psychosis
  - SI
  - Low motivation
  - Appetite problems
  - Trouble sleeping/Insomnia
- Bipolar Disorder
  - Increased energy
  - Decreased NEED for sleep
  - Increased goal directed activity
  - Delusions, grandiosity
  - Pressured speech
  - Flight of ideas

Anxiety Disorders

- Panic disorder
- OCD
- Generalized anxiety disorder

Other factors to consider

- Bowel/Bladder problems
- Pain/Physical discomfort
- Staff/peer conflict
- Social isolation
- Feeling ignored, disrespected
- Strange/unfamiliar environment

Agitation and Violence

- Close link between agitation and violence
- Staff often fearful of getting hurt by agitated pt
- Violent pts can also engender anger, powerlessness, hostility in staff, feelings of retaliation, desire to regain control at any cost

Violence amongst caregivers of elderly

- US health care workers: 16-25 injuries per 100 nursing staff a yr
- 33% caregivers reported violence towards them while caring for pt w/ dementia
- Sweden: 40% staff experienced violence over past yr, 18% noted daily episodes of violence

Risk factors for violence

- Staff
  - Less time of service
  - Male gender
  - Nursing home > Home care
  - Younger staff
- Patient
  - Substance use
  - Cognitive impairment
  - Poor impulse control
  - Depression
  - Poor health

Consequences of agitation

- Injury to self
- Falls
- Death
- Injury to staff or peers
- Isolation from staff or peers
- Victim of retaliatory violence by others

Management of Agitation

- Suspicion of delirium/medical illness
  - Prompt diagnosis and treatment of underlying medical illness
  - Avoid benzos (unless ETOH or sedative w/d)
  - Haldol: IV = 2x IM/PO dose
  - Atypicals: Quetiapine, Olanzapine, Risperidone
  - Help reorient pt
  - Return of proper sleep/wake cycle

Psychiatric Management

- Dementia
  - Cholinesterase Inhibitors, Memantine, Antipsychotics
- Bipolar disorder
  - Mood stabilizer, Antipsychotics, Benzos, ECT
- Major Depression
  - Antidepressants, Benzos, Antipsychotics, ECT
- Psychotic Disorders
  - Antipsychotics, Benzos
- Anxiety Disorders
  - Benzos, Antidepressants, Atypicals

Medications

- Benzodiazepines:
  - Lorazepam: Not hepatic metabolize, IV, IM, PO
- Mood Stabilizers:
  - Lithium, Depakote, Tegretol
- Antipsychotics:
  - Typical: Haldol (IM,IV,PO)
  - Atypical: Quetiapine, Risperidone, Olanzapine (IM), Ziprasidone (IM), Aripiprazole

Medications

- Recommend using medications if pt is becoming increasingly agitated and behavioral interventions are not working
- Try to use meds before pt gets out of control
- Scheduled is better than PRN

Behavioral Interventions

- Make pt feel safe, supported, and respected
- Remove objects that can be used as weapons
- Do not yell at pt and tell staff not to do so
- Set clear limits
- Give pt choices
- Use of multiple staff members to help physically redirect pt/show of force
- Utilize family, staff familiar to pt if appropriate
- Address basic needs: pain, hunger, comfort
- Let pt know that acting out will not be tolerated

Conclusion

- Aging effects how body handles medications
- Go slow and start low
- Think big picture
- What am I using this medication for?

Growing older