Age-Related Management of Psychological Issues in Older Adults

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Disclosures

- Dr. Forester serves on the Board of Directors of:
  - American Association for Geriatric Psychiatry
- Grants and Research Support Last Three Years:
  - NIMH
  - Rogers Family Foundation
  - AssureRx
  - Biogen
  - Eli Lilly
- Consulting Last Three Years:
  - Sunovion Pharmaceuticals, Inc.
  - Eli Lilly
  - INSYS Therapeutics, Inc.

Dr. Forester will discuss unapproved or investigational use of pharmaceutical compounds.

Learning Objectives

1. Differentiate the common behavioral syndromes in older adults including depression and neurocognitive disorders
2. Identify the impact of chronic health conditions on cognitive, behavioral and mental health
3. Describe evidence-based psychotherapeutic, behavioral and pharmacological treatments for depression and neurocognitive impairment in later life
4. Discuss the factors that contribute to improved adherence with recommended treatments

Outline

- General Principles of Geriatric Psychopharmacology
- Geriatric Depression - Management Strategies.
- Major and Mild Neurocognitive Disorders: Diagnosis, Biomarkers, Treatment and Prevention
- Management of the Behavioral and Psychological Symptoms of Dementia
- Risks Associated with Pharmacological Interventions
- Questions

Principles of Geriatric Psychopharmacology

1. Always develop a working diagnosis
2. Addition by subtraction
3. Start Low and Go Slow, BUT GO
4. Behavioral interventions and psychotherapy will augment treatment response

Case 1: Mrs. Anxiety

Mrs. Smith is an 82 year old recently widowed female, with a history of hypertension, COPD and peptic ulcer disease who presents to your office with recurrent low back pain, headaches, GI distress and nervousness. She is sleeping poorly and has lost about 10 pounds in the past two months. She is also concerned about increased forgetfulness. Mrs. Smith denies feeling depressed but has thoughts that life is not worth living this way.

Geriatric Depression: Overview

- Affects 6 million Americans over the age of 65
- 1 in 6 patients in primary care practice setting
- **NOT** a normal fact of aging – Beware of Ageism Bias
- Associated with Functional Disability and Suicide
- Can alter risk and course of general medical conditions
- Side effects directly affect compliance
- A recurrent disorder that can be treated and diagnosed in primary care setting

Risk Factors for Late Life Depression

- Medical illness
- Self-report of poor health and disability
- Pain; Use of pain medication
- Cognitive impairment
- Substance abuse
- Financial difficulties
- Bereavement
- Isolation; dissatisfaction with social network

Depression May Worsen Outcome of Many General Medical Conditions

Patient Population	Increased Morbidity	Increased Mortality
Post-MI[1,2]	√	√
CHF[3,4]	√	√
Nursing home patients[5]		√
Post-stroke[6]	√	

- **Depression also may worsen outcomes of cancer, diabetes, AIDS, and other disorders[7]**

1. Frasure-Smith N, et al. *JAMA.* 1993;270:1819-1825.
2. Penninx BW, et al. *Arch Gen Psychiatry*. 2001;58:221-227.
3. Jiang W, et al. *Arch Intern Med.* 2001;161:1849-1856.
4. Vaccarino V, et al. *J Am Coll Cardiol.* 2001;38:199-205.
5. Rovner BW, et al. *JAMA*. 1991;265:993-996.
6. Pohjasvaara T, et al. *Eur J Neurol*. 2001;8:315-319.
7. Petitto JM, Evans DL. *Depress Anxiety.* 1998;8(suppl 1):80-84.

Factors Contributing to Relapsing, Chronic Illness Course in Geriatric Depression

- Psychosocial factors:
  - Role transitions, bereavement, increasing dependency, interpersonal conflicts: RESPONDS WELL TO Interpersonal therapy (IPT)
- Progressive depletion of psychosocial and economic resources
- Chronic sleep disturbances
- Cerebrovascular Disease
- Neurodegenerative disorders
- Limited access to adequate treatment

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Tricyclic Antidepressatns

- **Amitriptyline, imipramine, nortryptyline, desipramine.**
- **Avoid as first line agents in elderly.**
- **Problems: orthostatic hypotension, anticholinergic SEs, cardiac conduction delays.**

SSRIs

- **Fluoxetine (Prozac)**
- **Sertraline (Zoloft)**
- **Paroxetine (Paxil)**
- **Citalopram (Celexa); Escitalopram (Lexapro)**
- **Fluvoxamine (Luvox)**

***First line treatments for late life depression**

***Downside: can be activating initially**

***Instant relief of anxiety unlikely**

***2011 FDA citalopram warning: dose-dependent QT prolongation > 20 mg/day elderly**

SNRIs (serotonin-norepinephrine reuptake inhibitors)

Duloxetine (Cymbalta)

- **DBPCT in patients 65+ demonstrates improved cognition and mood, well tolerated[1]**
- **Dose: 60 mg/day**
- **Adverse event discontinuation rates = to placebo**

Venlafaxine (Effexor)

- **At higher doses (150 mg +) acts on both NE/Serotonin**
- **Downside: follow BP especially at higher doses**
- **Few drug-drug interactions**

1. Raskin J et al. *Am J Psychiatry* 2007; 164: 900-909

NaSSA
(Noradrenergic and specific serotonergic antidepressant)

- Mirtazapine
  - Rapid improvement in sleep (antihistamine effect), anxiety (Blocks 5HT2 post synaptic receptor).
  - Few GI (5HT3 post synaptic blockade) and sexual side effects (5HT2 Blockade).
  - Common side effects: weight gain, sedation.
  - Antidepressant effect still takes 4-6 weeks and is more effective at higher doses (30-45 mg).
  - Mirtazapine (30 mg) plus fluoxetine (20 mg), venlafaxine (225 mg) or bupropion (150 mg) achieved greater remission rates (46-58%) after 6 weeks vs. fluoxetine monotherapy (20 mg) (25%). Mean age mid-40s.
  - Among those who responded, double blind discontinuation of one agent led to relapse in 40% of cases.[1]

1. Blier P, et al. Am J Psychiatry 2010; 167;281-288

Vortioxetine: Geriatric Depression

- Eight week, RCT: Vortioxetine 5 mg/day, duloxetine 60 mg/day (reference) versus placebo
- Mean age 70.6 years, mean baseline HAM-D24 score 29.0.
- Vortioxetine showed significantly ($p = 0.0011$) greater improvement on HAM-D compared with placebo at week 8 (3.3 points).
- Duloxetine also showed superiority to placebo at week 8, thereby validating the study.
- Cognition: Vortioxetine showed superiority to placebo on tests of processing speed (DSST), verbal learning and memory (RAVLT). Duloxetine superior to placebo on RAVLT only.
- Tolerability: withdrawal rate due to adverse events was 5.8%(vortioxetine), 9.9% (duloxetine) and 2.8% (placebo).

Katonah C et al. *Int Clin Psychopharmacol*. 2012; 27:215–223

Stimulants for Geriatric Depression

- Use remains controversial
- Effect is often rapid
- May be justified with:
  - apathy/psychomotor retardation
  - concurrent medical illness
  - intolerance of antidepressants
  - need for rapid response
- Effect can be lasting

Wallace et al 1995; Kaplitz 1975;Katon and Raskin 1980,
Pickett et al. 1990; Askinazi et al. 1986

Factors associated with poor adherence to psychotropic medication

- Medication side effects
- Poor insight into psychiatric illness
- Lack of readiness for treatment
- Negative attitudes toward medication
- Inadequate self-efficacy regarding symptoms
- Lack of social support

Magura S. Open Addict J. 2011 Nov 11; 4: 58–64.

Case 2: Mr. Sleepy

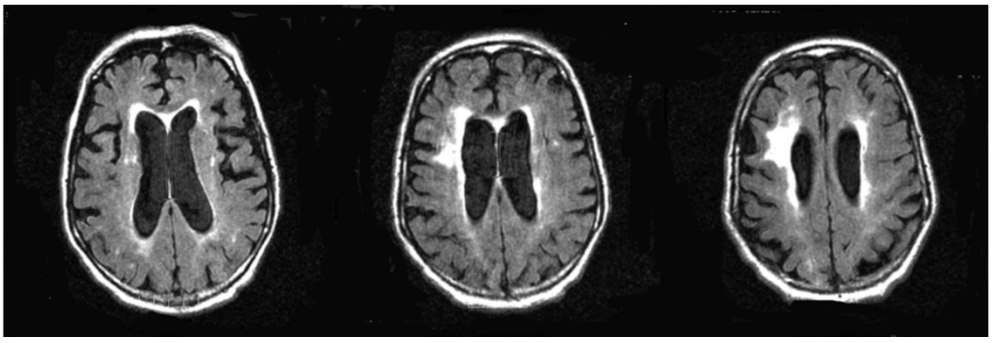
Mr. Sleepy is a recently retired 68-year-old man with type II diabetes mellitus, hypercholesterolemia, hypertension and intermittent alcohol use. He has no known prior psychiatric history. His family has observed that he is less interested in usual hobbies and spends his day sitting around the house mostly watching TV. Family reports that he is more irritable than usual. Mr. Sleepy tends to dismiss family's concerns, but does admit to poor motivation and low energy.

Depression/Executive Dysfunction Syndrome: Different Approach to Treatment?

- **Executive dysfunction (as measured by impaired initiation/perseveration (IP) on DRS) but not memory impairment predicted:**
  - **Delayed antidepressant response[1]**
  - **Greater risk of relapse, recurrence and symptom fluctuation following response[2]**
- **White matter hyperintensities predicted executive dysfunction[3,4] and poorer treatment response[4] (but not in all studies[5])**

1. Kalayam et al. 1999; 2. Alexopoulos et al. 2000; 3. Boone et al. 1992; 4. Hickie et al. 1995; 5. Salloway et al. 2002

MRI Illustration



Courtesy of Martin Goldstein MD

ECT

- **Geographic variation in usage.**
- **Likely underutilized in certain areas.**
- **Most effective treatment for severe depression, especially depression with psychosis.**
- **Think of ECT in patients with refractory depression plus not eating/suicidal.**

Psychotherapy for Geriatric Depression

- Highly effective especially in combination with pharmacotherapy
- Short-term therapies include:
  - Problem Solving Therapy (PST)
  - Interpersonal Therapy (IPT)
  - Cognitive Behavioral therapy (CBT)
- Improves adherence with pharmacotherapy

Conclusions Regarding Management of Geriatric Depression

- **Treat to remission, not response.**
- **If patients are partial responders at 6 weeks, they have a good chance to be full responders by 12 weeks: stay the course.**
- **If patients are partial responders at 12 weeks, despite adequate dose: change medications.**
- **Switching antidepressants is as effective as augmentation (about 50% will respond) but is associated with fewer side effects and lower costs.**
- **All patients, even those with first episodes, are candidates for at least one year, preferably two years of maintenance pharmacotherapy.[1]**
- **The dose that gets you well, keeps you well.**

1. NEJM 2006;354:1130-1138.
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Conclusions, Continued

- **Co-existing symptoms of anxiety pose risks for slow and incomplete response during acute treatment and for early recurrence during maintenance treatment. No evidence base for treating co-existing anxiety optimally in geriatric depression. Pay attention to residual symptoms of anxiety and poor sleep.**
- **Co-existing medical illness moderates response to long term treatment: patients with greater medical burden show more brittle recovery.**
- **Watch for caregiver depression: this also means burn-out in long term care clinicians**

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Major and Mild Neurocognitive Disorders

- Redefining the Diagnostic Criteria
- Biomarkers
- Treatment strategies
- Prevention
- Pharmacotherapy of Behavioral Disorders in Dementia

Alzheimer's Disease:

Redefining the Criteria

Pre-Clinical Alzheimer's Disease

MCI of Alzheimer's Disease

Dementia due to Alzheimer's Disease

Mild Neurocognitive Disorder: DSM 5

- Change in cognition
- Impairment in at least one cognitive domain
- Independence in functional abilities remain
- Cognitive assessment:
    - episodic memory impairment most frequent
- Etiology of MCI is consistent with AD pathology (rule out vascular, medical traumatic causes)
- Provide evidence of longitudinal decline
- Genetics consistent with AD (APOE4, PS1, PS2, APP)

Albert, M.S.et al. *Alzheimer´s & Dementia.* 2011;1-10

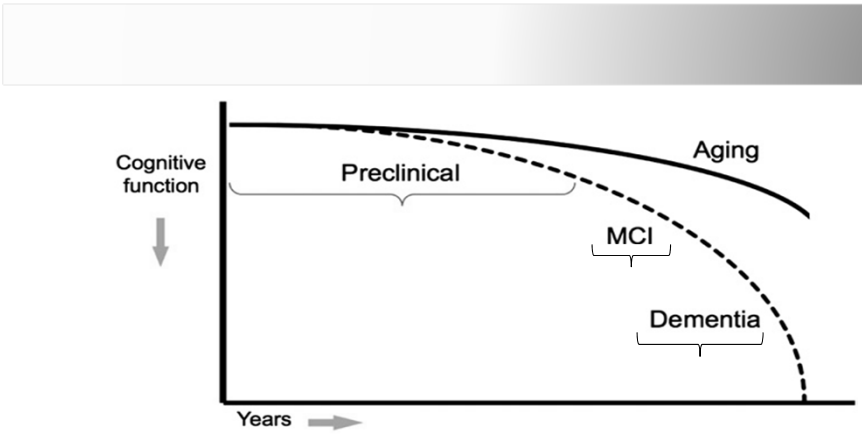
Major Neurocognitive Disorder: DSM 5

A. Evidence of significant cognitive decline from a previous level of performance in one or more areas of cognitive domains (complex attention, executive function, learning and memory, language, perceptual-motor or social cognition) based on:
    1. Concern of the individual, a knowledgeable informant or the clinician that there has been a significant decline in cognitive function; and
    2. Substantial impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment.
B. The cognitive deficits interfere with independence in everyday activities.
C. The cognitive deficits do not occur exclusively in the context of a delirium.
D. The cognitive deficits are not better explained by another mental disorder (e.g., major depressive disorder, schizophrenia).

Continuum of Alzheimer's Disease

Normal

Alzheimer's disease



Adapted from Sperling et al. 2011

PET Imaging

Positron Emission Tomography (PET)

- Fluorodeoxy-glucose (sugar) measures brain activity; decreased with dementia

- Amyloid tracers detect amyloid without autopsy; increased in Alzheimer's

AD

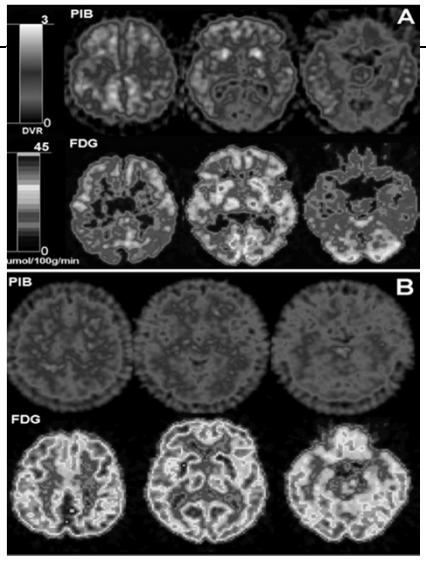
Amyloid

Sugar

Normal

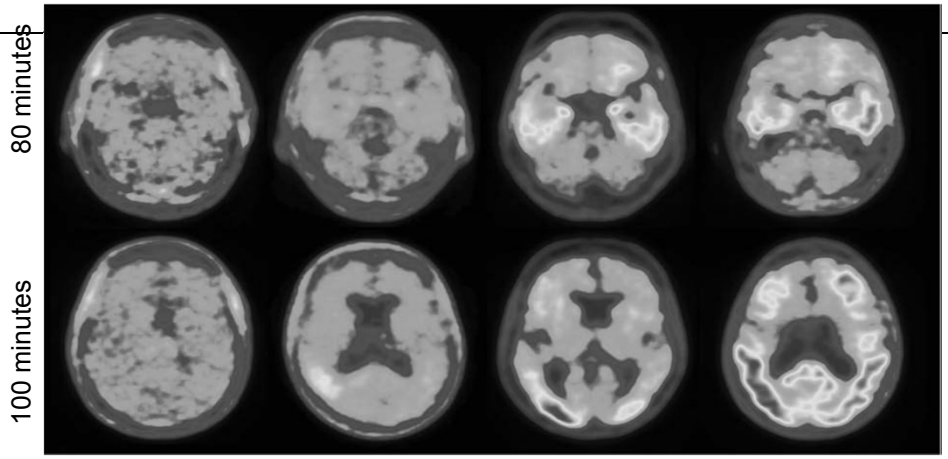
Amyloid

Sugar

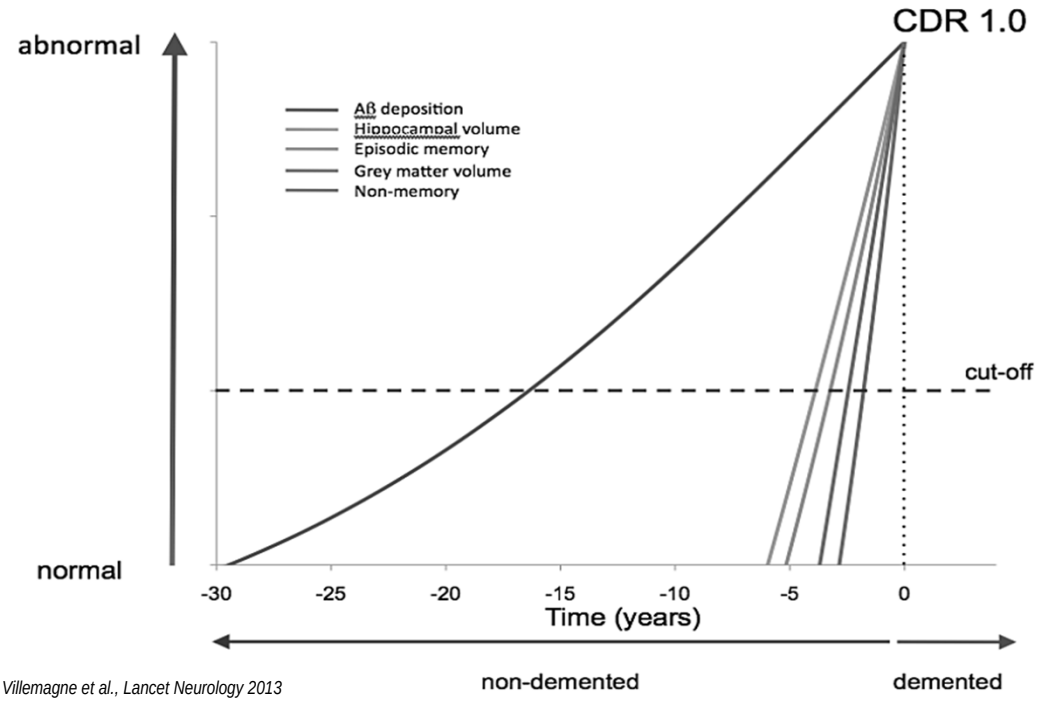


Li et al Eur J Nucl Med Mol Imaging. 2008 35(12): 2169–2181.

Alzheimer's disease: Tau Imaging



JT Chien et al. *Journal of Alzheimer's Disease* 2013



Villemagne et al., Lancet Neurology 2013

Irreversible Dementias

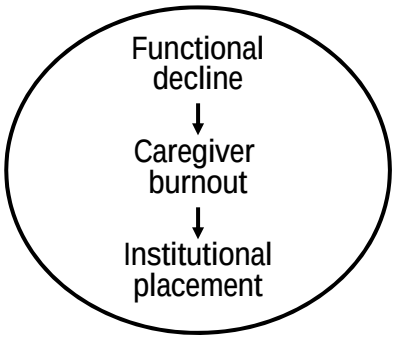
- **Alzheimer's disease**
- **Vascular Dementia**
- **Lewy Body Dementia**
- **Frontotemporal Dementias (Pick's disease)**
- **Creutzfeldt-Jakob disease**
- **Parkinson's disease**
- **Huntington's disease**
- **AIDS dementia complex**
- **Progressive aphasia**

Diagnostic Evaluation of Dementia

- **History from patient *and* relative or friend**
- **Clinical exam**
- **Blood work: CBC, Chem profile, Thyroid function tests, Syphilis serology, Vit B12, Folate**
- **Structural Brain Imaging: CT or MRI**
- **Neuropsychological testing**
- **Functional Imaging (SPECT or PET scan)**
- **EEG**
- **HIV Testing**
- **Genetics: APOE4**
- **CSF: tau, Amyloid beta 1-42**

Psychiatric Factors that Impact on the Trajectory of DAT

Psychosis
Delusions
Hallucinations
Social withdrawal



Cognitive deficits
Attention
Memory
Executive function

Mood disorder
Depression
Mania
Bipolar illness

Co-morbidity
Medical illness
Movement disorders
Substance abuse

Non-cognitive deficits
Aggressiveness
Agitation
Behavioral disturbance

The Cholinesterase Inhibitors: Indications and Uses

Medication	FDA Indication	Off-Label Uses
Aricept (donepezil)	Mild, moderate, and severe AD	***MCI** ***Non-AD dementias** **-DLB** **-Vascular** **-PD** **-Huntington's** **-FTD** **-Psychotropic-induced memory disturbance** **-ADHD** **-Attentional sx in PDD** **-Mania** **-Augmentation in negative symptom schizophrenia** **-TBI** **-ECT recovery**
Exelon (rivastigmine) Also patch	Mild to moderate AD	
Razadyne (galantamine)	Mild to moderate AD	

The Cholinesterase Inhibitors: Differentiating Characteristics

	Donepezil	Rivastigmine*	Galantamine and "ER"
Dosage Strengths (mg)	5,10,23 mg	1.5,3,6	4,8,12 ER: 8,16,24
Oral Solution	1 mg/ml	2 mg/ml	4 mg/ml
Starting Dose	5 mg q d	1.5 mg bid	4 mg bid
Maximum Recommended Dose	10 mg q d	6 mg bid	8 or 12 mg bid ER: 16 or 24 mg q d
$T_{½}$ (hours)	73	5	6 to 8
Plasma protein binding	96%	40%	18%
CYP450 substrate of	2D6/3A4	NA	2D6/3A4
CYP450 inhibitor of	NA	NA	NA

Exelon Patch: 4.6 mg/24 hours for 4 weeks, then 9.5 mg/24 hours, up to 13.3 mg/24 hours.

Clinical/Safety Issues

- **Before use, assess medical and psychosocial factors**
- **Side effects lower with slower titration**
  - **Common: nausea, vomiting, dyspepsia, anorexia, diarrhea, insomnia, fatigue, increased urination, cramps**
  - **Uncommon: syncope, bradycardia, confusion, depression, agitation**
- **Caution with liver/ gastric disease, COPD, bradycardia, inadequate supervision of adherence**
- **Dropout due to adverse event in 7-32% of patients in clinical trials (vs. placebo 1-8%)**

Goals of Therapy with Cholinesterase Inhibitors

- **Delay cognitive decline**
- **Delay functional decline**
- **Treat and/or prevent development of behavioral symptoms**
- **Don't expect a cure**
- **Downhill slope of illness will continue, yet quality of life may likely improve**

Memantine - NMDA antagonist

- **Approved in Europe 2002, U.S. October 2003**
- **Moderate affinity NMDA antagonist**
- **Half Life: 60-80 hours**
- **Renally excreted (serum level may rise with renal insufficiency and alkalinization of urine). Reduce dose by 50% in those with renal insufficiancy**
- **Minimal Hepatic P450 metabolism and interactions**
- **Dosing: 5 mg/day up to 10 mg twice daily over 4 weeks**
- **Rapid titration may escalate agitation**
- **Namenda XR 28 mg once daily dosage formulation:**
  - **7 mg/day up to 28 mg/day over 4 weeks**

Amyloid Immunotherapy: Aducanumab

- Biogen Phase Ib Trial reported March 20, 2015
- 166 subjects with mild AD
- Significant cognitive advantages on CDR-SB and MMSE after 54 weeks
- Highest dose produced greatest clinical benefit and highest percentage of ARIA-E (amyloid related imaging abnormalities-sulcal effusion)
- Phase III Trials to began Fall, 2015
- Clinical Trials Information:
  - http://www.alzforum.org/therapeutics

Preclinical Stages of AD

- Purpose: earlier intervention → reduced costs & delayed onset of clinical symptoms
- A hypothetical intervention that delayed the onset of AD dementia by 5 years would result in a 57% reduction in the number of patients with AD dementia, and reduce projected Medicare costs of AD from $627 to $344 billion dollars
- Therapeutic objective of preclinical studies is to treat pathological processes (e.g., lower Abeta burden or decrease neurofibrillary tangle pathology) to prevent subsequent neurodegeneration and eventual cognitive decline

Sperling RA, et al. *Alzheimer´s & Dementia.* 2011; 1-13

Amyloid Prevention Trials

- **Alzheimer Prevention Initiative (API)**
  - Colombian kindred (some US sites with PS-1)
  - 5 year trial – Clinical and Biomarker endpoints
  - Crenezumab
- **Dominantly Inherited Alzheimer Network (DIAN)**
  - PS-1, PS-2, APP mutations
  - 2 year Biomarker Trial – Adaptive design with 3 year clinical extension
  - Solanezumab, Gantenerumab, BACE inhibitor
- **Anti-Amyloid Treatment in Asymptomatic AD (A4) (ADCS)**
  - asymptomatic cognitively normal older adults. Biomarker evidence of disease used to enroll high risk individuals and follow treatment effects
  - Solanezumab

Case 3: Mr. Confused and Agitated

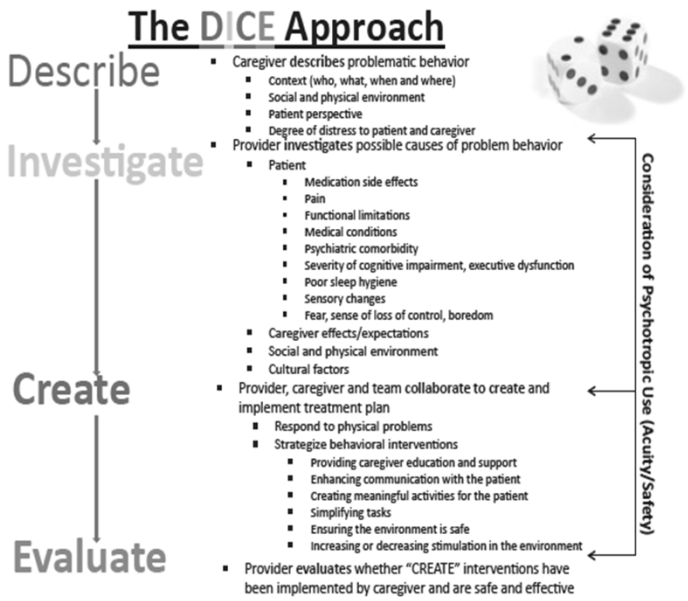
- 67 year old male, diagnosed with Alzheimer's Disease 6 years ago, living with wife at home, retired accountant
- Two month history of insomnia, irritability and physical restlessness and pacing especially late in the day
- One week of talking to "imaginary people in his home" and increased non-specific confusion per wife's report
- No significant past medical history
- Medications: Donepezil 10 mg per day, Memantine 10 mg twice daily, Mirtazapine 15 mg bedtime

Questions to Consider

- How would you describe/define these neuropsychiatric symptoms?
- How would you determine the etiology of these neuropsychiatric symptoms?
- What medical or neurological diagnoses may help explain the neuropsychiatric symptoms?
- What are the target symptoms to treat?
- What behavioral interventions may help?
- When would you intervene with pharmacotherapy and how would you choose specific pharmacological treatment strategies?

Behavioral Symptoms of Dementia Definitions

- **The Psychosis of AD (Jeste and Finkel)**
- **Neuropsychiatric Symptoms of AD**
- **BPSD (Behavioral and Psychological Symptoms of Dementia)**
- **Includes:**
  - **agitation, aggression, wandering, delusions, hallucinations, repetitive vocalizations, mood disturbances**



Kales et al. J Am Geriatr Soc 62:762–769, 2014.

Behavioral Interventions: First Line Treatment

- **Behavioral analysis: Identify precipitants and response**
- **Assure safety / Adequate supervision**
- **Treatment should not exceed patient's capacity to learn / remember**
- **Behavioral interventions can include:**
  - **Caregiver education**
  - **Prosthetic (habilitative) environment**
  - **Activity / exercise**
  - **Reminiscence therapies**
  - **Music therapy**
  - **Aromatherapy / massage**
  - **Bright light therapy**

Conventional Antipsychotics in Dementia

- Limited efficacy, substantial toxicity
- Associated with a risk of falls
- Cardiac toxicity (i.e., thioridazine)
- Associated with EPS
  - Parkinsonism (bradykinesia, rigidity, tremor)
  - Akathisia
  - Tardive dyskinesia: 28% after 1 year, 50% after 2 years, 63% after 3 years

Adapted from: Schneider LS, Pollock VE, Lyness SA et al. J Am Geriatr Soc. 1990(May);38(5):553-563

Atypical Antipsychotic Dosing in Dementia

- Risperidone: 0.5-2.0 mg/day
- Olanzapine : 2.5 mg-10 mg/day
- Quetiapine: 25 mg-200 mg plus per day
- Aripiprazole: 5-10 mg/day
- Clozapine, Ziprasidone, Paliperidone, Asenapine, Iloperidone, Lurasidone: Insufficient Data.
- TD incidence[1]:
  - Risperidone (1 mg/day): 1 year: 5.3%; 2 year: 7.2%
  - Olanzapine (4.3 mg/day):1 year: 6.7%; 2 year: 11%

1. Woerner MG, et al. *Neuropsychopharmacology*. April 2011

CATIE-AD Study

- **42 site, DBPCT, 421 Outpatients (including ALF residents) with AD and psychosis, aggression or agitation, 36 week study**
- **Randomized to:**
  - **Olanzapine (mean dose 5.5 mg/day)**
  - **Risperidone (mean dose 1.0 mg/day)**
  - **Quetiapine (mean dose 56.5 mg/day)**
  - **Placebo**

Schneider LS, Tariot PN et al. *NEJM* 2006;355:1525-1538

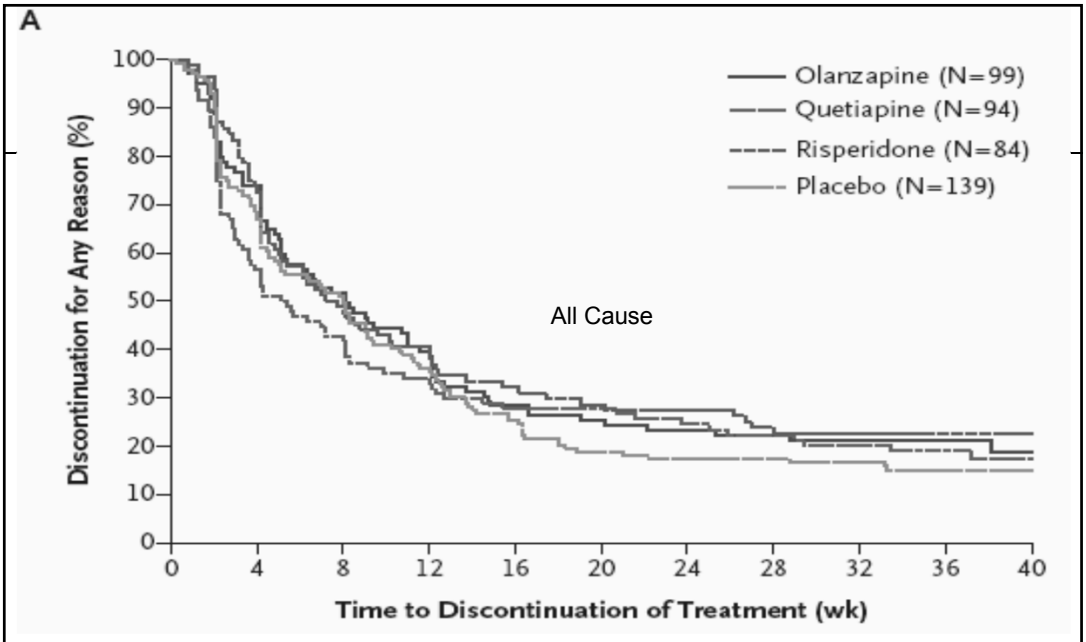


Figure 2. Discontinuation of Treatment in Phase 1 According to Study Group.

Schneider LS et al. NEJM 2006;355:1525-38.

CATIE-AD Secondary Outcomes Support Modest Beneficial Effect

- Significant difference between medications and placebo in time to discontinuation for inefficacy (P=0.002)
  - **Risperidone** **26.7 wk**
  - **Olanzapine** **22.1 wk**
  - **Quetiapine** **9.1 wk**
  - **Placebo** **9.0 wk**

Schneider LS et al. NEJM 2006;355:1525-38.

CATIE-AD: Side Effects

- **EPS: Olanzapine & risperidone > quetiapine**
- **Sedation: All drugs > placebo**
- **Confusion: olanzapine & risperidone > placebo**
- **Cognition: no worsening in any group**
- **Body weight: increased by all medications**
- **Prolactin: elevated with risperidone**
- **Falls: drugs = placebo**
- **CVA: 5/421 (1.1%): drugs = placebo**
- **Deaths: 7/421: drug=placebo**
- **Placebo less often discontinued due to adverse effects**

Schneider LS et al. NEJM 2006;355:1525-38.

Atypical Antipsychotics and Cerebrovascular Adverse Events

- **Class warning for elevated risk of cerebrovascular adverse events**
  - **Risperidone (3.8%) vs. Placebo (1.5%); N=1230**
  - **Olanzapine (1.3%) vs. Placebo (.4%); N=1882**
  - **Aripiprazole (1.3%) vs. Placebo (.6%); N=938**
  - **Quetiapine (0.3%) vs. Placebo (1.9%); N=568**
  - **Excellent Review:**
- Sacchetti, et al. Cerebrovascular Accidents in Elderly People Treated with Antipsychotic Drugs: A Systematic Review. Drug Saf 2010; 33 (4): 273-288.

FDA Warning on Mortality: Atypical Antipsychotics

- **Announced April 11, 2005**
- **Boxed Warning: atypical antipsychotics used to treat dementia-related psychosis carry an "increased risk of death compared with placebo"**
- **17 PCTs reviewed enrolling 5106 elderly pts with dementia related behavioral disorders**
- **Rate of death in drug treated patients was 4.5% vs. 2.6% in placebo group**
- **Risk of death 1.6 to 1.7 times that seen in placebo group**
- **Cause of death - heart related or infectious**
- **Four drugs involved in trials: aripiprazole, olanzapine, risperidone, quetiapine**
- **7 medications will have warning including clozapine, ziprasidone and Symbyax (olanzapine/fluoxetine)**
- **2008: Warning extended to conventional antipsychotics**

JAMA 2015: Mortality and Psychotropic Medication use in Dementia

- Aim: To determine the absolute mortality risk increase and number needed to harm (NNH) of antipsychotic, valproic acid and antidepressant use in patients with dementia relative to no treatment or antidepressant treatment
- Method: A retrospective case-control VA study, from 1998-2009. Participants were 90, 786 patients 65 years or older with a diagnosis of dementia
- Primary Outcome: absolute change in mortality risk and NNH over 180 days of follow-up in medication users and non-users

Maust DT et al. *JAMA Psychiatry.* March 18, 2015

Table 2. Crude Death Rates During a 180-Day Observation Period Among Patients With Dementia Starting Therapy With a New Medication

		Death, No. (%)			
Medication	No. of Pair[a]	Users	Nonusers	Risk Difference, % (95% CI)[b]	NNH (95% CI)[b]
Haloperidol	1921	398 (20.7)	162 (8.4)	3.8 (1.0 to 6.6)[c]	26 (15 to 99)
Olanzapine	1908	265 (13.9)	187 (9.8)	2.5 (0.3 to 4.7)[d]	40 (21 to 312)
Quetiapine	4621	545 (11.8)	378 (8.2)	2.0 (0.7 to 3.3)[c]	50 (30 to 150)
Risperidone	6338	883 (13.9)	538 (8.5)	3.7 (2.2 to 5.3)[c]	27 (19 to 46)
Valproic acid	901	110 (12.2)	65 (7.2)	4.1 (−1.0 to 9.2)	NA[e]
Antidepressant	29704	2472 (8.3)	2367 (8.0)	0.6 (0.3 to 0.9)[c]	166 (107 to 362)

3.5% higher mortality in high dose vs low dose group for all medications

Maust DT et al. *JAMA Psychiatry.* March 18, 2015

More Pragmatic Current Viewpoint: APA Practice Guideline for the Treatment of Patients With Alzheimer's Disease and Other Dementias (2nd Edition)

"Antipsychotics are the primary pharmacological treatment available for psychotic symptoms in dementia…considerable evidence from randomized, double-blind, placebo-controlled trials and meta-analyses for the efficacy of both first-generation and second-generation agents although this benefit is often modest…risks and benefits of these medications must be reassessed on an ongoing basis."

Rabins et al. Am J Psychiatry 2007;164(10 Suppl)

What's A Clinician to Do?

- Caution colleagues about over-reacting – alternative pharmacological choices (conventional antipsychotics, Benzodiazepines) not great evidence-base for efficacy and serious concern re tolerability
- Thorough assessment of etiology of BPSD is vital
- Always employ non-pharmacological strategies which must be studied in well designed clinical trials with and without pharmacotherapy
- When using antipsychotics: a careful informed consent with HCP/guardian required
- 2004 National Nursing Home Survey: 86% of antipsychotic medication use was off-label; 43% was non-evidence based[1]

Kamble P et al. *Psychiatric Services.* 2010;61:130–136

Antidepressants in Dementia with Agitation

- 6 RCTs with sertraline, citalopram, fluoxetine and trazadone
- Citalopram vs. Risperidone 12 week study for treatment of agitation and psychosis in hospitalized dementia patients.[1]
  - No efficacy differences on NBRS.
  - Equivalent EPS, more sedation with risperidone.
- CitAD Study: Citalopram more effective than placebo in treatment of agitation in dementia (NBRS). 3 weeks. Dosages greater than 20 mg/day associated with worsening cognition and QTc prolongation[2]
- DIADS-2 Study: sertraline not effective for depression in AD at 12 week or 24 week endpoints[3]

1. Pollack BG, et al. *Am J Geriatr Psychiatry. 2007; 15:942-952; 2.* Porsteinsson P et al. J*AMA*. 2014 Feb 19;311(7):682-913;. *3.*Weintraub D. et al. *Am J Geriatr Psychiatry*. 2010; 18(4):332-340

RESEARCH ARTICLE

International Journal of Geriatric Psychiatry

Safety and utility of acute electroconvulsive therapy for agitation and aggression in dementia

Deepa Acharya[1,2], David G. Harper[1], Eric D. Achtyes[3], Stephen J. Seiner[4], Jack A. Mahdasian[3], Louis J. Nykamp[3], Lesley Adkison[5], Lori Van der Schuur White[3], Shawn M. McClintock[6,7], Manjola Ujkaj[4], Donald A. Davidoff[8] and Brent P. Forester[1]

Table 1 Demographics and clinical characteristics ($n = 23$)

	Mean (SD)	*N* (%)
Age	73.8 (9.2)	
Education	13.9 (2.6)	
Gender		
Female	n/a	14 (60.1)
Race		
Caucasian	n/a	23 (100)
Diagnoses	n/a	
Alzheimer's disease		13 (56.5)
Vascular dementia		4 (17.4)
Mixed dementia		2 (8.7)
Frontotemporal dementia		1 (4.3)
Dementia NOS		3 (13.0)
No. ECT treatments	9.4 (range: 5–14)	
RUL		17 (73.9)
RUL to BL		2 (8.7)
BL		4 (17.4)
No. of days on unit pre-ECT	27.9 (20.1)	
Total no. of days on unit	57.3 (28.2)	
Continuation ECT recommended	n/a	15 (65.2)

NOS, not otherwise specified; ECT, electroconvulsive therapy; RUL, right unilateral; BL, bilateral; n/a, not applicable.

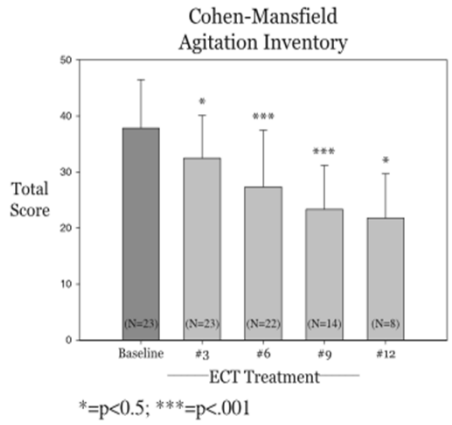


Figure 1 Cohen-Mansfield Agitation Inventory.

Acharya D et al. *Int'l J Geriatric Psychiatry* 2015 Mar;30(3):265-73.

Dronabinol for the Treatment of Agitation and Aggressive Behavior in Acutely Hospitalized Severely Demented Patients with Noncognitive Behavioral Symptoms

Matthew R. Woodward, B.A.,
David G. Harper, Ph.D.,
Arkadiy Stolyar, M.D.,
Brent P. Forester, M.D., M.Sc.,
James M. Ellison, M.D., M.P.H.

40 inpatients with dementia complicated by agitation

Treated with dronabinol up to 10 mg/day (mean dose 7 mg/day) for 17 days

Significant reduction on Pittsburgh Agitation Scale (PAS) total scores and subscales of physical and verbal agitation/resisting care ($p<0.0001$)

No adverse effects led to drug discontinuation

Sedation (n=9), delirium (n=4), urinary tract infection (n=3), and confusion (n=2) most frequent AEs

Woodward MR et al. *American Journal of Geriatric Psychiatry.* 2014 Apr;22(4):415-9.

Benzodiazepines

- Minimal efficacy data
- Sedating
- Further inhibit learning and memory
- Cause falls
- Paradoxical disinhibition

Summary

Geriatric Depression

- **Often subsyndromal with higher prevalence rates in medically compromised individuals**
- **Associated with high morbidity and mortality in conjunction with co-morbid medical illness**
- **SSRIs, SNRIs, Mirtazapine treatments of choice**
- **Short term psychotherapies effective (CBT, IPT, PST)**

Major and Mild Neurocognitive Disorders

- **Early diagnosis is key**
- **Treatment to 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**