Therapy Update: Managing Dementia, Delirium, and Depression in Older Individuals

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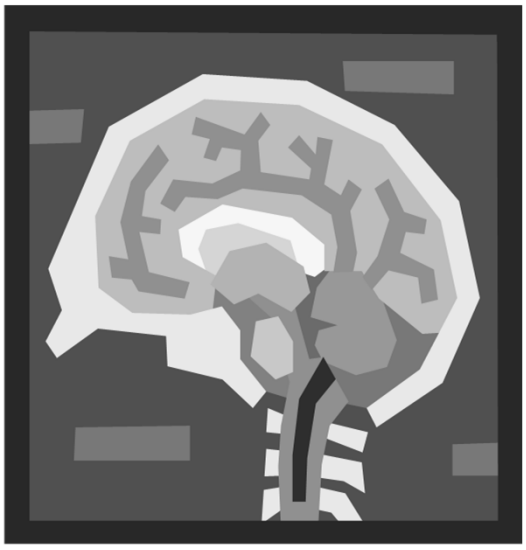
Presentation Objectives

Upon completion of this presentation participants will be able to:

- **Identify options for treating cognitive and behavioral symptoms in dementia and delirium.**
- **Compare both positive and negative outcomes associated with medications used to treat dementia and delirium.**
- **Apply options for treating initial and treatment resistant depression in older individuals.**

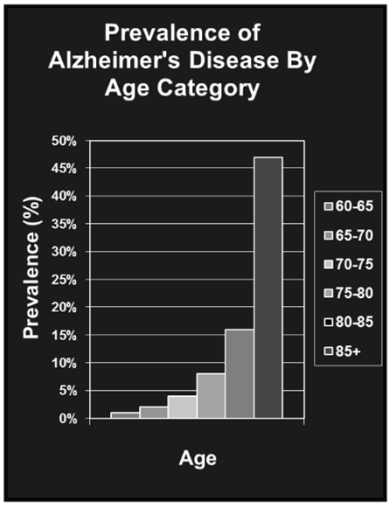
"If the brain was simple enough for us to understand it, we would be too simple to understand it."

Ken Hill



Epidemiology of Dementia

- **Alzheimer Disease (AD) accounts for most cases of dementia**
- **15% of Americans >68 have dementia**
- **6th leading cause of death; 5th leading cause in elders**
  - **5.8 million Americans suffer from AD**
  - **Prevalence increases with age**
    - **Approximately 5% of US population 65 to 74**
    - **Nearly 50% of those 85 y/o and older**



(Adapted from: https://www.alzheimersdisease.com)

JAMA. 2019;322(16):1589-1599. doi:10.1001/jama.2019.4782

Risk Factors for Developing Dementia

- Non-modifiable
  - Female sex
  - Black race
  - Hispanic ethnicity
  - Genetic factors (ex. APOE gene)
- Modifiable
  - Hypertension
  - Diabetes
  - Diet
  - Limited cognitive, physical, social activities

JAMA.2019;322(16):1589-1599.doi:10.1001/jama.2019.4782

Impact of Dementia on Society

- Cost to economy
  - Direct health care costs
    - Hospitalization and physician visits
    - Long term care
    - Home care
    - Medications
  - Indirect costs
    - Lost wages
    - Care-giver burden

Differentiating Dementias

- Typical Aging - AACI
  - Recent memory for important events intact
  - Occasional difficulties with word finding
  - ADLs intact; normal performance on MSE
- Mild Cognitive Impairment - MCI
  - Memory complaints only
  - ADLs intact; minimal changes in other areas
  - High risk of progression to dementia
    - 50% progress to dementia within 5 years

Zanni GR, Wick JY. Differentiating Dementias in Long-Term Care Patients. The Consultant Pharmacist. 2007;22(1):14-28.
JAMA.2019;322(16):1589-1599.doi:10.1001/jama.2019.4782

Differentiating Dementias

- Alzheimer's Disease (AD)
  - Most common form of dementia
  - Slow onset and continued cognitive decline
  - Symptoms
    - Short-term memory impairment
    - Language difficulties
    - Loss of executive function
      - Abstract thinking, reasoning, planning
    - Mood and personality changes
    - Psychiatric and behavioral symptoms (late stages)
    - Extrapyramidal features, e.g. bradykinesias (late stages)

Zanni GR, Wick JY. Differentiating Dementias in Long-Term Care Patients. The Consultant Pharmacist. 2007;22(1):14-28.

Differentiating Dementias

- Vascular Dementia (VaD)
  - New term: VCID – vascular contribution to cognitive impairment
  - Past term: Vascular Cognitive Impairment (VCI) or multi-infarct dementia
  - Patient aware of deficits
  - Focal neurologic signs
  - Temporal relationship with "event" or vascular pathology and risks (HTN, DM, Smoking)
  - Abrupt deterioration with stepwise progression
  - Executive dysfunction, depression, apathy, behavioral changes more prevalent than in AD

Zanni GR, Wick JY. Differentiating Dementias in Long-Term Care Patients. The Consultant Pharmacist. 2007;22(1):14-28.

Differentiating Dementias

- Lewy Body Dementia (DLB)
  - Cytoplasmic inclusions in substantia nigra (dopamine and Ach deficits)
  - Beta-amyloid/senile plaques occur, but not neurofibrillary tangles
  - Dementia with prominent extrapyramidal motor symptoms early in disease (PD with dementia)
    - Rapid eye movement may be noted for years prior to cognitive impairment
    - Neuroleptics may worsen symptoms or cause life-threatening dyskinesias and neuromalignant syndrome
  - Fluctuating mental and physical status
    - Hallucinations and "parkinsonism"
    - Apathy, depression, visual-spatial impairment, verbal-blocking common

Zanni GR, Wick JY. Differentiating Dementias in Long-Term Care Patients. The Consultant Pharmacist. 2007;22(1):14-28.

Differentiating Dementias

- Frontotemporal Dementia
  - Prominent personality changes with disinhibition and apathy common
  - Deterioration of social skills and reduced verbal output with spared drawing and calculation abilities
  - Variable effect on memory
  - Typical therapies (AChIs) may worsen symptoms

Zanni GR, Wick JY. Differentiating Dementias in Long-Term Care Patients. The Consultant Pharmacist. 2007;22(1):14-28.

Etiology of Alzheimer's Disease

- Early Onset (5%)
  - Amyloid Precursor Protein
  - Presenilin 1
  - Presenilin 2
- Late Onset
  - Apo E4 genotype
- Environmental factors
- Neuropathologic changes
  - Cortical and limbic atrophy
  - Neurotransmitter degeneration
  - B-amyloid neuritic plaques
  - Neuofibrillary tangles (phosphorylated tau protein)

Pathophysiology

- Inflammatory Mediators
- Cholinergic Hypothesis
- Other neurotransmitter abnormalities
- Neurotoxins
  - Superoxides
  - Increased NMDA activity
  - Others
- Comorbid diseases
- Evolving Hypotheses

Clinical Features

- Deterioration in function
  - Decreased basic ADLs
    - Bathing, toileting, dressing, feeding oneself
  - Decreased IADLs
    - Managing finances, shopping, cooking, cleaning, maintaining independent lifestyle
- Behavioral disturbances
- Cognitive impairment
- Decline in global function

Delirium, Dementia & AMI

- Age-Associated Memory Impairment
  - Normal aging (slip of tongue, word searching)
  - Should not affect functioning
- Dementia
  - Chronic cognitive deterioration
  - Progressive
- Delirium
  - Acute confusional state
  - Altered consciousness
  - Reversible

10 Warning Signs of Dementia

1. Memory loss effects job skills
2. Difficulty performing familiar tasks
3. Problems with language
4. Disorientation to time/place
5. Poor judgment
6. Problems with abstract thinking
7. Misplacing things
8. Changes in mood or behavior
9. Changes in personality
10. Loss of initiative

Diagnosis – Dementia

- An acquired impairment in multiple areas of intellectual function:
  - Impaired short or long-term memory plus
  - Impaired language, praxis, object recognition, or executive function
- Impaired occupational or social functioning or impaired interpersonal relationships
- Represents a decline in function
- Not reversible
- Not secondary to delirium
- Must differentiate between other metabolic and psychiatric illnesses

From: DSM-V

Delirium: Overview

- Also called 'encephalopathy' or 'metabolic encephalopathy'
- Core Symptoms
  - Disorientation
    - Date, time, place
  - Confusion
  - Memory dysfunction
  - Altered level of consciousness
  - Impaired attention
  - Fluctuating course
    - Key in differentiating from dementia

Delirium: Overview

- Possible Symptoms
  - Anxiety
  - Agitation
  - Hallucinations—especially visual
  - Apathy and withdrawal
  - Sleep disturbances
  - Emotional lability
  - Perceptual disturbances
  - Neurologic signs

Gleason OC, Am Fam Physician 2003;67(5):1027-34

Delirium

- Present in up to 50% of hospitalized elderly patients
- 8-17% on admission; 40% of NH residents
- Increased risk of negative outcomes:
  - Increased length of stay
  - Functional decline
  - Nursing home/rehab center placement
  - Mortality
  - Increased costs (direct and indirect)

Risk Factors:
- Dementia or other cognitive impairment
- Functional impairment
- Sensory impairment
- Substance abuse
- Advanced age
- Comorbidity
- Stroke, depression, medical disorders, infection

Inouye KS, et al. Lancet 2014;383:911-22.

Delirium Subtypes

Hyperactive – Mixed – Hypoactive

Hyperactive

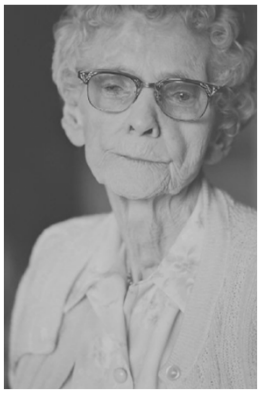
Agitated
Disoriented
Delusional
Hallucinations
Adverse events
Injury—falls
Pulling on IVs
and catheters

Hypoactive

Subdued
Quietly confused
Disoriented
Apathetic
Often unrecognized
Confused with
depression,
dementia,
or pseudodementia

Delirium Summary

- Acute, fluctuating cognitive impairment
- Sign of an underlying medical condition
  - Primary treatment to address this condition
- Symptomatic treatments can help
- Environmental management can help



Drugs That May Induce Delirium

High Risk	Moderate Risk	Lower Risk
Antidepressants (esp. tricyclics)	Alpha-blockers	ACEIs
Antipsychotics	Antiarrhythmics	Anti-Asthmatics (theophyline)
Dopaminergic Drugs	Beta-blockers	Antibacterials
Opioid Narcotics	Digoxin	Anticonvulsants
Benzodiazepines	NSAIDs	Calcium Channel Blockers
Corticosteroids	Postganglionic Blockers	Diuretics
Lithium		H_2 Antagonists
Alcohol Withdrawal		

Borovicka and Fuller. Delirium. In: Tisdale and Miller eds. Drug-Induced Diseases: Prevention, Detection, and Management. 2005. American Society of Health-System Pharmacists. Bethesda, MD.

Drugs with Unexpected AntiAch Activity

Results – of the top 24 medications prescribed in the elderly, 13/24 exhibited detectable anticholinergic activity

Cimetidine	(0.86)	Isosorbide	(0.15)
Prednisolone	(0.55)	Warfarin	(0.12)
Theophylline	(0.44)	Codeine	(0.11)
Digoxin	(0.25)	Dipyridamole	(0.11)
Nifedipine	(0.22)	Triamterene	(0.08)
Ranitidine	(0.22)	Captopril	(0.02)
Furosemide	(0.22)		

Tune, et al, *Am J Psychiatry* 1992;149:1393

Effect of Anticholinergics on Hospitalization in Elders

From Taiwan's Longitudinal Health Insurance Database

- **Results (in young old population - 65-74 y/o)**
- **Odds ratio (adjusted) for negative outcome with increasing ACB score (from 1 to ≥4)**

Outcome	O.R. ACB = 1	O.R. ACB ≥4
Emergency department visits	1.41	2.25
All-cause hospitalizations	1.32	1.92
Fracture specific hospitalizations	1.10	1.71
Incident dementia	3.13	10.01

Wen-Han Hsu, et. al. Comparative Associations Between Measures of Anticholinergic Burden and Adverse Clinical Outcomes. *Ann Fam Med* 2017;15:561-569.

Assessing Anticholinergic Potential for Commonly Used Medications

- **Anticholinergic Risk Scale (ARS)**
  - **Rudolph JL, Salow MJ, Angelini MC, McGlinchey RE. The anticholinergic risk scale and anticholinergic adverse effects in older persons. Arch Intern Med. 2008; 168(5): 508-513.**
- **Anticholinergic Cognitive Burden Scale (ACB)**
  - **Boustani M, Campbell N, Munger S, Maidment I, Fox C. Impact of anticholinergics on the aging brain: a review and practical application. Aging Health. 2008; 4(3): 311-320.**
- **Drug Burden Index - Anticholinergic component (DBI-Ach)**
  - **Hilmer SN, Mager DE, Simonsick EM, et al. A drug burden index to define the functional burden of medications in older people. Arch Intern Med. 2007; 167(8): 781-787.**

Wen-Han Hsu, et. al. Comparative Associations Between Measures of Anticholinergic Burden and Adverse Clinical Outcomes. *Ann Fam Med* 2017;15:561-569.

Assessing Anticholinergic Potential for Commonly Used Medications

- **Anticholinergic Risk Scale (ARS)**
- **Anticholinergic Cognitive Burden Scale (ACB)**
- **Drug Burden Index - Anticholinergic component (DBI-Ach)**
- **Supplementary materials: http://www.AnnFamMed.org/content/15/6/561**

Drug	ADS	ACB	ARS	Drug	ADS	ACB	ARS
alprazolam	---	1	---	chlorpheniramine	3	3	3
amantadine	1	2	2	chlorpromazine	3	3	3
aminophylline	1	---	---	chlorprothixene	3	---	---
amitriptyline	3	3	3	chlorthalidone	1	1	---
amoxapine	3	3	---	cimetidine	2	1	2
aripiprazole	---	1	---	citalopram	1	---	---
asenapine	---	1	---	clemastine	3	3	---
atenolol	---	1	---	clidinium	3	1	---
atropine	3	3	3	clomipramine	3	3	---
azatadine	3	---	---	clonazepam	1	---	---
azathioprine	1	---	---	clorazepate	1	1	---
azelastine nasal	1	---	---	clozapine	3	3	2
baclofen	---	---	2	codeine	---	1	---
barberry	1	---	---	colchicine	---	1	---
benztropine	3	3	3	cyclobenzaprine	2	2	2
bromocriptine	1	---	---	cycloserine	1	---	---
brompheniramine	3	3	---	cyclosporine	1	---	---
buproprion	---	1	---	cyproheptadine	3	2	3
captopril	1	1	---	darifenacin	3	3	---
carbamazepine	---	2	---	desipramine	3	3	2
carbidopa	---	---	1	desloratadine	---	1	---

Wen-Han Hsu, et. al. Comparative Associations Between Measures of Anticholinergic Burden and Adverse Clinical Outcomes. *Ann Fam Med* 2017;15:561-569.

Delirium Management Strategies

Intervention	Examples of Intervention Strategies
Medication Adjustments	Reduce/discontinue CNS acting medications such as anticholinergics, sedative/hypnotics, opioids
Acute Medical Issues	Infection, rehydration, hypoxia
Reorientation	Eyeglasses, hearing aids, daytime lighting, family, pictures
Safe Mobility	Early mobilization, avoid restraints, 'in-room sitters'
Sleep-Wake Cycle	Provide uninterrupted sleep (avoid sedatives) Reduce daytime napping, consider earplugs
Pharmacological Management	Severe agitation - Low doses of antipsychotics (haloperidol 0.25-0.5 mg PO or IM BID or atypical antipsychotics) Alcohol withdrawal - Benzodiazepines

Barr J, et al. CritCare Med 2013;41:263-306

Antipsychotics in Delirium

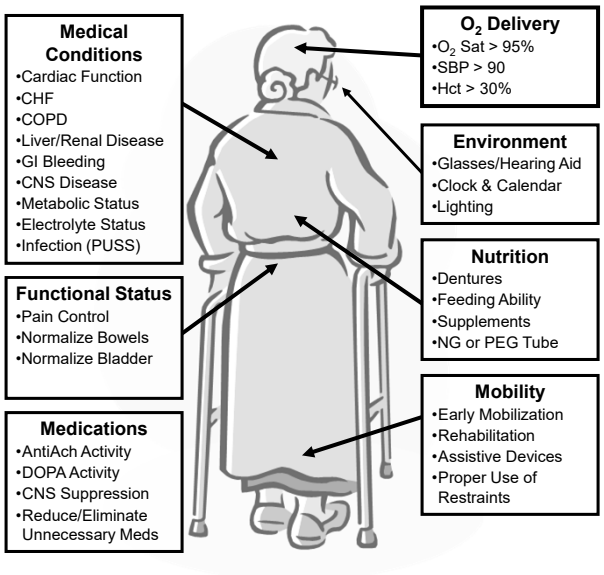
- **Minimal evidence to support use of antipsychotics in delirium**

Medications	Considerations
Haloperidol	• Available PO, IM, and IV (off-label); Caution QTc prolongation with IV • Potent D2 antagonist; Higher rates of EPS (less so in delirium)
Chlorpromazine	• Available PO, IM; IV must be administered over 30 minutes • QTc prolongation, highly anticholinergic; risk of orthostasis
Quetiapine	• Supported by SCCM guidelines • Weak D2 antagonist, only available PO
Risperidone	• Stronger D2 antagonist, only available PO for acute use
Olanzapine	• Available PO and IM; anticholinergic • Caution using IM in combination with BZDs - ↑ mortality
Ziprasidone	• PO requires food for absorption, Available IM • QTc prolongation

Barr J, et al. CritCare Med 2013;41:263-306

Delirium Summary

Developing an Organized Approach to the Prevention and Treatment of Delirium after Hip Fracture



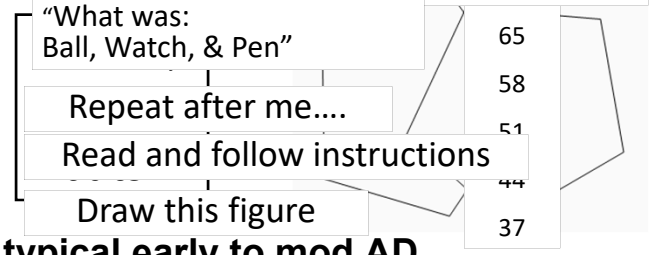
Robertson and Robertson. J Bone Joint Surgery. 2006;88A(9):2060-8.

Diagnosing Dementia

- Screening methods
  - MMSE
  - MINI-COG
  - Functional Activities Questionnaire
  - 7-Minute Screen
  - Others
- Diagnostic tests
  - Toxic-metabolic
  - Neuroimaging

Folstein Mini-Mental Status Examination

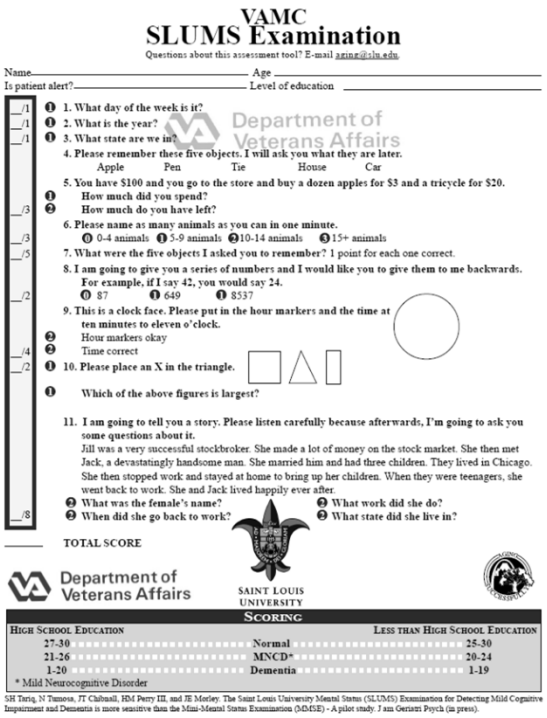
- Orientation — Give season/date/day/month/year hospital/floor/town/state/country — 100
- Registration — Identify three objects by name and ask to repeat – Ball, Watch, & Pen — 93
- Attention and calculation — Count backward from 100 by 7's — 86
- Recall — "What was: Ball, Watch, & Pen" — 65
- Language — Repeat after me…. — 58
- Read and follow instructions — 51
- Scoring — Draw this figure — 44
  - 10 to ~28 typical early to mod AD — 37
  - < 24 indicates need for detailed exam



Folstein M, Folstein S, McHugh P. *Mini-Mental State. A practical method for grading the cognitive state of patients for the clinician.* J Psych Res 1975;12:189–198.

Clinical Assessment of Cognition

- **St. Louis University Mental Status (SLUMS) Examination**



VAMC
SLUMS Examination

Questions about this assessment tool? E-mail azinz@slu.edu

Name_____ Age _____
Is patient alert?_____ Level of education _____

1. What day of the week is it?
2. What is the year?
3. What state are we in?
4. Please remember these five objects. I will ask you what they are later.
   Apple Pen Tie House Car
5. You have $100 and you go to the store and buy a dozen apples for $3 and a tricycle for $20.
   How much did you spend?
   How much do you have left?
6. Please name as many animals as you can in one minute.
   0 0-4 animals 1 5-9 animals 2 10-14 animals 3 15+ animals
7. What were the five objects I asked you to remember? 1 point for each one correct.
8. I am going to give you a series of numbers and I would like you to give them to me backwards. For example, if I say 42, you would say 24.
   0 87 1 649 1 8537
9. This is a clock face. Please put in the hour markers and the time at ten minutes to eleven o'clock.
   Hour markers okay
   Time correct
10. Please place an X in the triangle.
    Which of the above figures is largest?
11. I am going to tell you a story. Please listen carefully because afterwards, I'm going to ask you some questions about it.
    Jill was a very successful stockbroker. She made a lot of money on the stock market. She then met Jack, a devastatingly handsome man. She married him and had three children. They lived in Chicago. She then stopped work and stayed at home to bring up her children. When they were teenagers, she went back to work. She and Jack lived happily ever after.
    What was the female's name?
    When did she go back to work?
    What work did she do?
    What state did she live in?

TOTAL SCORE

Department of Veterans Affairs

SAINT LOUIS UNIVERSITY

Scoring		
High School Education		Less than High School Education
27-30	Normal	25-30
21-26	MNCD*	20-24
1-20	Dementia	1-19

* Mild Neurocognitive Disorder

SH Tariq, N Tumosa, JT Chibnall, HM Perry III, and JE Morley. The Saint Louis University Mental Status (SLUMS) Examination for Detecting Mild Cognitive Impairment and Dementia is more sensitive than the Mini-Mental Status Examination (MMSE) - A pilot study. J am Geriatri Psych (in press).

Progression of Dementia

Years	2					10
MMSE	25	20	15	10	5	0

Stage **Mild** **Moderate** **Severe**

Mild	Moderate	Severe
• Memory loss • Mild anomia • Poor drawing • Mood swings • Mild executive dysfunction • Mild personality changes	• Unable to learn new information • Aphasia, apraxia, agnosia • Wandering, agitation, aggression, psychosis, confusion, insomnia • Need ADL assistance	• Gait changes • Incontinence • Motor disturbances • Unable to do ADLs • Bed or chair bound • Need for LTC placement

Adapted from Fitten 2005

Key Issues in Dementia Treatment

- Eliminate or minimize drug-related adverse reactions
- Address concurrent diseases that resemble or complicate treatment
- Improve cognitive performance and treat related symptoms such as psychiatric and behavioral disturbances

Treatment of Dementia

- Relies on early recognition and accurate diagnosis
- Goals
  - Improving cognition
  - Possibly delaying progression
  - Managing psychiatric and behavioral manifestations
- Patient and family support

Nonpharmacologic Treatment

- Cognitively stimulating activities
- Physical exercise
- Social interactions with others
- Healthy diet (e.g. Mediterranean diet)
- Adequate sleep (e.g. uninterrupted and sufficient hours)
- Proper personal hygiene
- Safety (inside and outside the home (e.g. driving)
- Medical and advanced care directives
- Long-term healthcare planning
- Financial planning
- Effective communication (e.g. expressing needs and desires)
- Psychological health (e.g. meaningful activities, music)

JAMA.2019;322(16):1589-1599. doi:10.1001/jama.2019.4782

Other Nonpharmacological and Communication Strategies

- Simplify demands and tasks
- Avoid confrontation & frustration
- Remain calm, firm, supportive
- Consistent environment; avoid changes
- Provide reminders, explanations, & cues
- Recognize declines; adjust expectations
- Report sudden declines
- Respite care for care givers

Faulkner, et al. 2005

Treatment Guidelines (AAN)

- AChE Inhibitors – use throughout illness; indicated in mild to severe disease
- NMDA Inhibitors – indicated in moderate to severe disease
- Antiamyloid therapies - aducanumab
- Therapy for noncognitive symptoms
  - Antipsychotics
  - Mood stabilizers
  - Antidepressants
  - Sedatives/hypnotics

Cholinesterase Inhibitors

- Mechanism: reduce hydrolysis of acetylcholine after release by presynaptic neurons – increases Ach
- Class ADRs –
  - GI – Nausea, vomiting, diarrhea, anorexia
  - CNS – sedation or insomnia
  - CV – bradycardia (like vagal effect)
- Examples:
  - Physostigmine
  - Tacrine
  - Donepezil
  - Rivastigmine
  - Galantamine

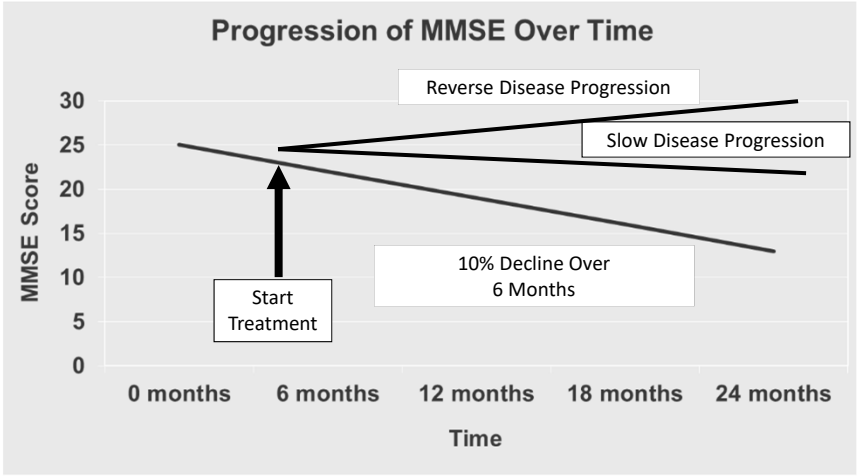
Cholinesterase Inhibitors

- Donepezil
  - Lowest rates of nausea, vomiting and anorexia; increased with 23 mg dose
  - Long half-life favors once daily dosing; compliance
  - Approved for mild, moderate and severe dementia
  - Available in combination with memantine
- Rivastigmine (also inhibits butyrylcholinesterase)
  - Available in transdermal form
    - Reduces nausea and approved for mild, moderate and severe dementia
  - Oral form approved for mild, moderate dementia
  - Only ChEI approved for Parkinson's dementia
- Galantamine
  - Approved for mild-moderate dementia only
  - Greatest risk of CPY interactions
  - IR form requires BID dosing

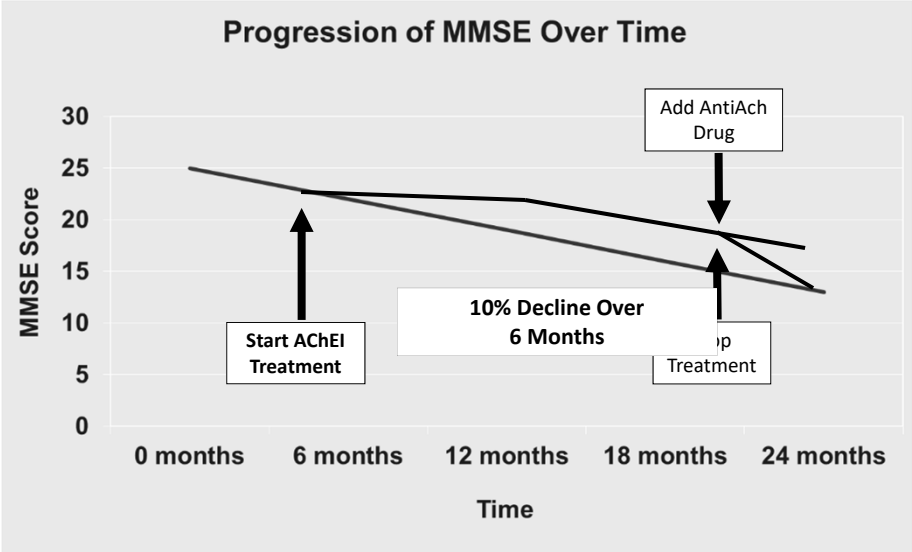
Measuring Treatment Effectiveness

- Alzheimer Disease Assessment Scale: Cognitive Subscale (ADAS-Cog)
- Clinician Interview-based Impression of Change scale and Clinical Global Impression of Change scale (CIBIC)
- Folstein Mini Mental Status Examination (MMSE)

Models of Treatment Response



Models of Treatment Response



Cholinesterase-inhibitor General Statements

- "Palliative treatments"
- Small but measurable benefits
  - Symptom progression delayed by approximately 4 to 9 months in most studies
- Adverse effects vary considerably
- Longer half-life benefits noncompliant patients
- Efficacy established in mild to moderate disease
- Discontinued due to ADRS or lack of efficacy

N-Methyl-D-Aspartate Antagonists (NMDA)

- Memantidine (Namenda®) –
  - Characteristics
  - Indication – moderate to severe AD
  - Dosing
    - Initial dose 5mg once daily. Increase dose in 5mg increments at weekly intervals.
    - IR: Target dose of 20 mg daily
    - ER Doses available: 7mg, 14mg, 21mg, 28mg
    - Available in combination with donepezil – lower ChEI-adverse effects (less anorexia, n/v)
    - Reduce dose with moderate renal impairment.
  - ADRs
    - Headache, dizziness, drowsiness/confusion, agitation/anxiety, increased BP, seizure risk(?)
- Memantine + Donepezil (Namzaric®)
  - 7-10, 14-10, 21-10, 28-10

Aducanumab (Aduhelm)

- Recombinant human immunoglobulin G1 (IgG1) monoclonal antibody
- Designed to promote clearance of cerebral amyloid aggregates and insoluble forms of Aβ
- Provisional approval by FDA in June 2021
- Considerable controversy – limited efficacy and significant
- Approval "based on reduction in Aβ plaques observed in patients treated with Aduhelm" rather than compelling evidence of a change in clinical measures"

Day GS, Scarmeas N, Dubinsky R, et. al. Aducanumab Use in Symptomatic Alzheimer Disease Evidence in Focus 2022:98(15);619-31.

Aducanumab Summary

- **Expected benefit**
  - Reduces cerebral amyloid plaques measured by amyloid PET.
  - Unknown if improvements in function, cognition, quality of life, maintenance of independence, or survival.
- **Risks**
  - Amyloid-related imaging abnormalities with edema/effusionARIA-E in 41% of patients
  - 25% with ARIA had symptoms (approximately 10% overall); most resolved with drug cessation
  - Other common risks - headache, confusion, dizziness, and nausea.
  - AE-associated decreases in cognition, quality of life, independence, and survival possible
- **Commitment/burden**
  - Need to see a specialist to be assessed for treatment
  - Confirmation of elevated amyloid via a specialized brain scan (amyloid PET, not covered by Medicare or most insurers) or lumbar puncture with CSF testing (currently covered)
  - Requires infusions every 4 weeks at specialized centers
  - Brain MRIs needed prior to initiation and then twice within the next year or more)
  - At least 16 days/year to complete evaluations, investigations, and infusions
  - Suspected AEs may require substantially greater commitment.
- **Cost**
  - Estimated drug cost = $28,000/year or more
  - Additional costs - pretreatment evaluations, follow-up visits, investigations, and drug infusion

General Statements on Dementia Therapies

- Modest evidence of ChEIs in mild to moderate AD and memantine for moderate to severe AD
- Higher doses of donepezil not clinically superior
- Higher doses of transdermal rivastigmine may show greater benefit
- Recent trials with memantine in mild-moderate AD not clinically beneficial
- Newer trials show slight or unclear benefit when memantine added to ChEIs
- Updated evidence on safety of ChEIs
  - Anorexia, weight loss, falls, hip fractures, syncope, bradycardia, and increase pacemakers

Rabins PV, et al. American Psychiatric Association 2014
http://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/alzheimerwatch.pdf

Supplements

- Ginkgo biloba
  - Antioxidant, neurotrophic, antiinflammatory properties
  - Efficacy (Le Bars et al. 1997) - 12 months in 236 patients; 2.4% decrease in ADAS-Cog; No change in CGIC; 50% withdrawal in treatment group, 38% in placebo
  - Meta-analysis (Oken et al. 1998) = Improves cognitive function “slightly”; most studies inadequately controlled
- Huperzine A: AchEI-like activity
  - Additive effects with AChI’s, neuroprotectant effects?
- Curry spice (curcumin)
- Others

Treatment Decisions in Dementia

- When to initiate treatment?
- When to combine therapies?
- When to add and what adjunct therapies to add?
- When to stop cognitive therapies?
- When to withdraw other therapies?

Discontinuing Cholinesterase Inhibitors in Patients with Dementia

- Stopping therapy recommended:
  - Non-adherence
  - Continued deterioration
  - Terminally ill or serious comorbidity
  - Patient or caregiver choice
- Domino Trial (2012):
  295 patients with mod/severe AD on donepezil ≥ 3 months (MMSE and Bristol ADL scale)
  - Continued donepezil → ~ 32% less decline
  - Switch to memantine → less pronounced decline (~ 20% less)
  - Addition of memantine → no additional benefit
  - Discontinuation of donepezil → worsening condition

Winslow BT, et al. Am Fam Physic 2011;83(12):1403-12.
Howard R et al, NEJM 2012; 366(10):893-903

Behavioral and Psychological Symptoms of Dementia (BPSD)

- Behavioral disturbances are common
  - ≥ 80% of patients with AD will experience agitation
  - ~ 40% of patients with AD experience aggression
- Assessment requires going back to the ABC's
  - Antecedents–
    - What triggered the behavior?
    - Assess for pain or other modifiable contributors to symptoms
  - Behavior–
    - What type of behavior?
    - Is it a target for intervention?
  - Consequences–
    - To whom? The patient or others?
    - Serious episodes may result in discharge to another level of care

Reus VI, et al. Am J Psychiatry 2016;173:543

Neuropsychiatric Symptoms

- Hallucinations
  - Auditory/Visual
- Delusions
  - Persecutory
  - Theft
  - Infidelity
  - Capgras syndrome
- Anxiety
  - Agitation/Combative
  - Restlessness, others
- Psychomotor activity
  - Wandering/Pacing
  - Purposeless activity
- Personality
  - Disengagement
  - Disinhibition
  - Emotional blunting
- Mood Changes
  - Depressive symptoms
  - Elevated mood
  - Mood lability
- Miscellaneous
  - Appetite changes
  - Sleep Disturbances
  - Changes in sexual activity

BPSD Clusters, Symptoms & Consequences

Cluster	Symptoms	Consequences
Depression	Sadness, crying, hopelessness, guilt, anxiety	Poor self care Weight loss
Apathy	Withdrawal, lack of pleasure	Isolation, reduced self-care & hygiene
Aggression	Resistance to care; physical or verbal	Altercations Injuries
Psychomotor agitation	Wandering, pacing, sleep disturbances, repetitive actions, intrusiveness	Escaping (exiting/eloping), Altercations
Psychosis	Delusions, hallucinations	Isolation Refusal of care

Reus VI, et al. Am J Psychiatry 2016;173:543

Psychotic Symptoms in Elders

- **Symptoms of psychosis common**
  - **Community-dwelling elders – 0.2% to 4.75%**
  - **LTC residents – 65% or higher**
- **Antipsychotic prescribing common**
  - **Often used for BPSD**
  - **Very old (>85) very likely to be prescribed antipsychotics (20%), benzodiazepines, and antidepressants**

Chahine LM, et al. The elderly safety imperative and antipsychotic usage. Harv Rev Psychiatry 2010;18:158-172.

Concerns with Use of Psychotropics in Dementia

- Typical adverse effects
  - Somnolence and altered cognition
  - Falls
  - Anticholinergic effects
  - Hypotension
  - Dystonias
- Serious adverse effects
  - Sudden death, stroke
  - Pneumonia and hospitalizations
  - Parkinsonism and tardive dyskinesia
  - Neuroleptic malignant syndrome and serotonin syndrome
- Other effects
  - Weight gain, diabetes, metabolic syndrome
  - Bone marrow suppression
  - Infections
  - Seizures
  - Hormonal disturbances
  - Altered thermoregulation
  - Cataracts
  - Sexual dysfunction and priapism

Chahine LM, et al. The elderly safety imperative and antipsychotic usage. Harv Rev Psychiatry 2010;18:158-172.

Scope of the Problem

- Inspector General Report – May 2011
  - 14% of the 2.1M elderly LTC residents had Medicare claims for atypical antipsychotics in 2007
  - 83% of claims for atypical antipsychotic drugs for 'off-label' conditions
  - 88% associated with conditions specified in recent FDA black-box warning
  - 51% of claims considered erroneous (costing $116M of $309M spent on LTC antipsychotic prescriptions)
  - 22% not administered in accordance with CMS standards for unnecessary drugs

Medicare Atypical Antipsychotic Drug Claims for Elderly Nursing Home Residents. EOI-07-08-00150. May 2011.

Strategies for Controlling BPSD – Avoiding Use of Antipsychotics

Medication	Targets	Evidence
Cholinesterase Inhibitors	Agitation, aggression, anxiety, delusions	Mixed/modest
Anticonvulsants	Agitation, aggression, mood lability	Lacking 2014 guidelines suggest modest benefit with carbamazepine Recommended against valproic acid
Antidepressants	Depression, apathy, agitation, aggression, anxiety	Cit-AD citalopram 30 mg Case reports with trazodone up to TID
Buspirone	Anxiety, behaviors	Small positive study; Dose 25.7 mg ±12.5

http://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/alzheimerwatch.pdf
Madhusoodanan S, et al. World J Psychiatr2014; 4(4):72-9; Freund-Levi Am J GeriatrPsychiatr2014;22(4):341-8.; Rodda J, et al. Intpsychogeriatr2009; 21(5):813-824.; Tariotet al. JAGS 2001;49:1590-9. Feldman H, et al. Neurol2001;57:613-20; RabinsPV. APA Guideline 2014 ; Freund-Levi Am J Geriatr Psychiatry 2014;22(4):341-8; Porsteinsson AP. JAMA 2014;
Santa Cruz, MR. IntPsychogeriatr2017; 26:1-4

FDA Warning on ALL Antipsychotics

- **"Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death"**
- **Meta-analysis of 17 placebo-controlled trials rate of death: (modal duration 10 weeks)**
  - **Antipsychotic-treated mortality = 4.5% vs. placebo=2.6%**
  - **1.6-1.7 times increased mortality risk vs. placebo-treated**
- **Primary causes of mortality:**
  - **Cardiovascular: heart failure, sudden death**
  - **Infectious: pneumonia (aspiration)**
- **Antipsychotics are NOT approved for dementia-related psychosis**

Prescribing information of Antipsychotics (both first generation and second)
www.dailymed.nlm.nih.govion)
Schneider LS. Arch Neurol2011;68(8):991-8.
http://www.choosingwisely.org

Fall Risk with Antipsychotic Use in the Elderly

- **FDA Labeling Update in February 2017; Warnings section**
- **Somnolence, postural hypotension, motor or sensory instability, may lead to falls or injury (including fracture)**
- **Risk of orthostasis mediated by α1 antagonism**

Low	Moderate	High
Aripiprazole Ziprasidone Haloperidol	Risperidone Quetiapine	Clozapine Iloperidone Chlorpromazine

Antipsychotic Risks in the Elderly

Medications	FGAs - Greatest Risk	SGAs - Greatest Risk
Sedation	Low potency – chlorpromazine	Quetiapine
Parkinsonism	High potency – haloperidol, fluphenazine	Risperidone
Akathisia	High potency	Aripiprazole, lurasidone
Metabolic	Low potency	Olanzapine, clozapine
Orthostasis	Low potency	Quetiapine, clozapine
QTc prolongation	Thioridazine, pimozide, haloperidol IV	Ziprasidone, quetiapine, clozapine
Severe neutropenia		Clozapine

Antipsychotic Use in the Elderly APA 2016 Recommendations

- Benefits should outweigh risks
- Low initial dose and titrate to lowest effective dose
- Gradual Dose Reduction (GDR)
  - After 4 weeks if no improvement
  - After 4 months with response
  - Recurrence of symptoms with GDR indicates continued treatment warranted
- Monitor for relapse for at least 4 months after discontinuation

Reus VI, et al. Am J Psychiatry 2016;173:543-6.

Antipsychotic Use in Elders with Movement Disorders

- Parkinson's Disease, Parkinson's Disease Dementia, or Lewy-Body Dementia
- Increased risk of EPS with antipsychotics
- Avoid high-potency antipsychotics – esp. haloperidol
- Consider use of quetiapine or clozapine (non-FDA use)
  - Clozapine: monitor Absolute Neutrophil Count (ANC) weekly for first 6 months; every 2 weeks for next 6 months; then monthly thereafter
- Pimavanserin (Nuplazid)
  - FDA approved for Parkinson's disease psychosis
  - Not approved for psychosis in dementia

Panchal SC, et al. Curr Psychiatry Reports 2018;20:3; Bozymski KM, et al. Ann Pharmacother2017;51:479-87. www.clozapinerems.com

Dextromethorphan & Quinidine (Nuedexta)

- NMDA receptor antagonist (dextromethorphan) plus enzymatic inhibitor (quinidine) indicated for pseudobulbar affect
- Used 'off label' for agitation/aggression in Alzheimer Disease and other dementias
- Considered 'potentially inappropriate' in AGS Beers Criteria

Dementia Clinical Pearls for BPSD

- Assess for pain, infection - rule out delirium
- Remove delirium-associated medications
- Employ behavioral interventions
- Educate caregivers and staff
- Add cholinesterase inhibitor
- Consider antidepressant
- If no other options remain…consider an antipsychotic
- Discuss benefit vs. risk and reevaluate continued use (every 6 months OR every 4 months per American Psychiatric Association)

DeMers S, et al. Med Clin NA. 2014; 98:1145–1168. Reus VI, et al. Am J Psychiatry 2016;173:543-6.
Sink K. et al. JAMA 2005;293(5):596–608.

Nonpharmacologic Approaches

- Environmental manipulation
  - Safe, consistent environment
  - Moderate stimulation
  - Contrasting colors
  - Pictures for directions
  - Structured routine
  - Familiar personal objects
  - Orientation cues (clocks, calendars)
  - Clear simple communication

Sutor 2001

Nonpharmacologic Approaches

- Simple behavioral techniques
  - Validation
  - Don't correct misstatements
  - Encourage active participation in care
  - Psychotherapy
    - Emotion-oriented, supportive, interpersonal, reminiscence therapy
  - Stimulation-oriented therapy
    - Music, art, pets, exercise

General Recommendations

- Anxiety – SSRI antidepressant or buspirone
- Psychotic symptoms – antipsychotics
  - Acute psychosis – haloperidol commonly used in hospitals; other atypicals also used
  - Subacute/Chronic psychosis – atypical agents
    - Quetiapine (25-200 mg/day)
    - Risperidone (0.25 to 2 mg/day)
    - Olanzapine (2.5 to 5 mg/day)
    - Clozapine (for refractory, contraindications, Parkinson's dementia)
  - Agitation with psychosis – same

General Recommendations

- Aggression and anger (without psychosis); “stabilize mood” –
  - (mild/acute) – trazodone (highly sedating)
  - (mild/longer term) - divalproex, trazodone, SSRI, carbamazepine, buspirone
  - (severe/acute) - high-potency antipsychotic (quetiapine, risperidone, haloperidol)
  - (severe/longer term) - divalproex, high potency antipsychotic (quetiapine, risperidone, pimavancerin?)

Conventional Antipsychotics

- Modest efficacy (<20%)
- Haloperidol –
  - High risk of EPS, sedation
  - Low AntiAch effects
- Chlorpromazine, others
  - High risk of AntiAch, dysrhythmias, hypotension, sedation, & EPS effects
- All antipsychotics considered potentially inappropriate drugs (Beers List) in absence of psychiatric symptoms (delusions, paranoia, psychosis)

Beers MH. Explicit criteria for determining potentially inappropriate medication use by the elderly: an update. Arch Intern Med 1997;157:1531-6.
Fick DM, et. al. Updating the Beers criteria for potentially inappropriate medication use in older adults: results of a US consensus panel of experts. Arch Intern Med 2003;163:2716-24.

Atypical Antipsychotics – Adverse Effects

- Class effects of concern
  - CNS – somnolence, confusion, anti-ACh effects, EPS, parkinsonism, neuromalignant syndrome
  - Metabolic syndrome – weight gain, increased glucose, lipid abnormalities
  - CV – hypotension, orthostasis, thromboembolism, CVA, sudden death
- Special considerations
  - Clozapine – agranulocytosis (lower EPS & parkinsonism risk)

Assessing Risk of Use of Atypical Antipsychotics

- Cardiovascular/cerebrovascular adverse events and death
  - Documented risk
  - May be higher with conventional agents
  - RR vs. placebo 1.54 (C.I.= 1.06-2.23); AR 3.5 cases per 100 patient years
- Sedation – falls and accidental injuries
- Metabolic effects
  - Weight gain, diabetes, dyslipidemia
- Movement disorders
- Anticholinergic effects

Schneider LS, et.al. Risk of Death with Atypical Antipsychotic Drug Treatment for Dementia: Meta-Analysis of Randomized Placebo-Controlled Trials. JAMA 2005;294:1934-43
Wang PS, et.al. Risk of Death in Elderly Users of Conventional vs. Atypical Antipsychotic Medications. N Engl J Med 2005;353(22):2335-41
Hartikainen S, et.al. The Use of Psychotropics and Survival in Demented Elderly Individuals. Int Clin PsychoPharm 2005;20:227-31

Chronic Antipsychotic Use

- Re-evaluate use/dose every 3-6 months
- Taper dose twice yearly
- Risk may likely outweigh benefit*
- Risk of tardive dyskinesia and other movement disorders^
  - Typical antipsychotics – 5.24 cases of TD per 100 person-years
  - Atypical antipsychotics – 5.19 cases of TD per 100 person-years

*Schneider LS, et al. Effectiveness of Atypical Antipsychotic Drugs in Patients with Alzheimer's Disease. N Engl J Med 2006;355(15):1525-38
^Lee PE, et al. Antipsychotic Medications and Drug-Induced Movement Disorders Other Than Parkinsonism: A Population-Based Cohort Study in Older Adults. J Am Geriatr Soc 2005;53:1374-9.

Dementia Management "Pearls"

- Choosing appropriate therapeutic interventions
- Monitoring response
- Escalating or withdrawing therapy
- Managing behavioral and psychiatric complications
- Treating non-neurologic illnesses in patients with dementia
- Managing adverse reactions and drug interactions

TREATMENT OF DEPRESSION

Key Concepts – Depression

- Follow Treatment Guidelines
- Rule out medical causes of depression and drug-induced depression
- Treatment goal
  - Resolution of current symptoms (remission)
  - Prevention of further episodes (relapse or recurrence)
- Adverse effects might occur immediately; resolution of symptoms can take 2 to 4 weeks or longer.
- Adherence is essential for successful outcome

VandenBerg AM. Major Depressive Disorder. In: DiPiro JT, Yee GC, Posey L, Haines ST, Nolin TD, Ellingrod V. eds. *Pharmacotherapy: A Pathophysiologic Approach, 11e* New York, NY: McGraw-Hill; . http://accesspharmacy.mhmedical.com/content.aspx?bookid=2577&sectionid=234138584. Accessed February 09, 2020.

Key Concepts – Depression

- Antidepressants considered equally efficacious
  - Other factors guide selection (age, side effects, past response)
- Evaluating response
  - Target signs and symptoms
  - Quality-of-life issues (roles, social functioning, occupational function)
  - Tolerability
- Evaluating inadequate response
  - Adequate dose
  - Adequate duration
  - Medication adherence

Teter CJ, Kando JC, Wells BG. Chapter 51. Major Depressive Disorder. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey L. eds. Pharmacotherapy: A Pathophysiologic Approach, 9e. New York: McGraw-Hill; 2014. http://accesspharmacy.mhmedical.com/content.aspx?bookid=689&Sectionid=45310502.

Treatment Phases

- *Acute* phase
  - 6 to 10 weeks
  - Goal is remission (absence of symptoms)
- *Continuation* phase
  - 4 to 9 months after remission achieved
  - Goal to eliminate residual symptoms or prevent relapse (return of symptoms within 6 months of remission)
- *Maintenance* phase
  - 12 to 36 months after remission
  - Goal to prevent recurrence (separate episode of depression); some require lifelong treatment

Risk of Recurrence

- Increases with increased number of past episodes
- Duration of antidepressant therapy depends on the risk of recurrence
- Some recommend lifelong maintenance therapy for those at greatest risk for recurrence
  - Younger than 40 years of age with two or more prior episodes
  - Patients of any age with three or more prior episodes

Epidemiology

- True prevalence unknown
- The National Comorbidity Survey Replication
  - 16.2% of the population had history of major depressive disorder in lifetime
  - > 6.6% had an episode within past 12 months
- Women at increased risk
  - Lifetime rate 1.7 to 2.7 x Males
- Highest rates in adults 18 to 29 y/o
- Prevalence in elderly (65 to 80 y/o)
  - 20.4% in women
  - 9.6% in men

Pharmacologic Therapy

- General comments
  - Antidepressants show equivalent efficacy when administered in comparable doses
  - Cannot predict which antidepressant will be most effective in an individual patient
  - Failure to respond to one antidepressant class or one agent within a class not predictive of failure to another class or another drug within the class
  - 65% to 70% improve with drug therapy, compared to 30% to 40% improvement with placebo

Pharmacologic Therapy

- Empiric initial choice based on:
  - History of response
  - Pharmacogenetics (history of familial antidepressant response)
  - Concurrent medical history
  - Presenting symptoms (e.g., fatigue vs. psychomotor agitation)
  - Potential for drug-drug interactions
  - Adverse events profile
  - Patient preference
  - Drug cost
  - Several antidepressants on BEER's List (!)

Selective Serotonin Reuptake Inhibitors (SSRIs)

- Efficacy superior to placebo and comparable to other classes major depression
- SSRIs generally chosen as first-line antidepressants due to safety in overdose and improved tolerability
- Available agents:
  - Citalopram (Celexa®)
  - Escitalopram (Lexapro®)
  - Fluoxetine (Prozac®)
  - Fluvoxamine (Luvox®)
  - Paroxetine (Paxil®) (!)
  - Sertraline (Zoloft®)
  - Vortioxetine (Trintellix®)

Available Antidepressants

Selective Serotonin Reuptake Inhibitors (SSRIs)			
Drug	**Brand Name**	**Initial Dose (mg/day)**	**Usual Dosage Range (mg/day)**
Citalopram	Celexa	20	20–40*
Escitalopram	Lexapro	10	10–20*
Fluoxetine	Prozac	20	20–60
Fluvoxamine	Luvox	50	50–300
Paroxetine(!)	Paxil	20	20–60
Sertraline	Zoloft	50	50–200
Vortioxetine	Trintellix	5	5-20
Fluoxetine+ Olanzapine	Symbyax		

- **All SSRI's considered on AGS BEERs Criteria as 'Fall-Risk' drugs**
- **FDA recommends 20mg maximum dose in elderly for citalopram and 10 mg for escitalopram due to risk of ↑QT interval**

Mixed 5HT and NE Reuptake Inhibitors

- **Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs) – (Recommended over TCAs)**
  - **Venlafaxine (Effexor®) & desvenlafaxine (Pristiq®)**
    - **Inhibits 5-HT reuptake at low doses, with additional NE reuptake at higher doses**
  - **Duloxetine (Cymbalta®)**
    - **Both 5-HT and NE reuptake inhibition across all doses**
- **Some studies suggest SNRIs associated with higher rates of response and remission than other antidepressants**
  - **Most involved venlafaxine and not all studies support this conclusion**
- **2019 BEERS list added SNRI's as 'fall-risk'**

Aminoketones

- **Bupropion (Wellbutrin®)**
  - **Unique among all currently available antidepressants**
  - **No appreciable effect on 5-HT reuptake**
  - **Demonstrates reuptake properties at both the NE and DA reuptake pumps**

Available Antidepressants

Newer-generation Serotonin & Norepinephrine Reuptake Inhibitors			
Drug	Brand Name	Initial Dose (mg/day)	Usual Dosage Range (mg/day)
Desvenlafaxine	Pristiq	50	50
Duloxetine	Cymbalta	30	30–90
Venlafaxine	Effexor	37.5–75	75–225

Norepinephrine and Dopamine Reuptake Inhibitor (NDRI)			
Bupropion	Wellbutrin	150	150–300

Triazolopyridines

- Effective agents in major depression; carry risks that limit usefulness
- Act as both 5-HT_2 receptor antagonists and 5-HT reuptake inhibitors
- Can also enhance 5-HT_{1A}-mediated neurotransmission
- Trazodone (Desyrel®)
  - Blocks α-1 adrenergic and histamine receptors - increased side effects (e.g., dizziness and sedation)
- Nefazodone (Serzone®)
  - Use as an antidepressant has declined
  - Reports of hepatic toxicity caused FDA-required black box warning

Mixed Serotonin-Norepinephrine Effects

- Mirtazapine (Remeron®)
  - Enhances central NE and 5HT activity
    - Antagonism of central presynaptic adrenergic autoreceptors and heteroreceptors
  - Antagonizes 5-HT_2 and 5-HT_3 receptors
    - Lower anxiety and gastrointestinal side effects
  - Also blocks histamine receptors
    - Sedative properties (especially at low doses)
  - Mild appetite stimulation properties

Available Antidepressants

Mixed Serotonergic Effects (Mixed 5-HT)			
Drug	Brand Name	Initial Dose (mg/day)	Usual Dosage Range (mg/day)
Nefazodone	Serzone	100	300–600
Trazodone	Desyrel; Oleptro	50	150–300
Vilazodone	Viibryd	10	40

Serotonin and α_2-Adrenergic Antagonist			
Mirtazapine	Remeron	15	15–45

Mixed 5HT and NE Reuptake Inhibitors

- **Tricyclic Antidepressants**
  - **Increase NE and 5-HT activity by blocking reuptake**
  - **Effective in all depressive subtypes**
  - **Use diminished due to availability of equally effective and safer therapies**
  - **Frequent adverse effects**
  - **Representative agents:**
    - **Amitriptyline (Elavil®) (!)**
    - **Desipramine (Norpramin®) (!)**
    - **Imipramine (Tofranil®) (!)**
    - **Nortriptyline (Pamelor®) (!)**

Available Antidepressants

Tricyclic Antidepressants (TCAs)			
Drug	Brand Name	Initial Dose (mg/day)	Usual Dosage Range (mg/day)
Amitriptyline(!)	Elavil	25	100–300
Desipramine(!)	Norpramin	25	100–300
Doxepin(!)	Sinequan	25	100–300
Imipramine(!)	Tofranil	25	100–300
Nortriptyline(!)	Pamelor	25	50–150

Monoamine Oxidase Inhibitors

- **Increased NE, 5-HT, and DA through inhibition of metabolism by monoamine oxidase (MAO) enzymes**
- **Chronic therapy alters receptor sensitivity**
  - **Down-regulation of β-adrenergic, α-adrenergic, and serotonergic receptors - similar to TCAs**
- **Nonselective MAO-A and MAO-B inhibitors**
  - **Phenelzine (Nardil®) and tranylcypromine (Parnate®)**
- **Selective MAO-B inhibitors**
  - **Selegiline (Eldepryl®, Ensam®, Zelapar®)**
    - **Recently approved transdermal patch allows inhibition of MAO-A and MAO-B in the brain with reduced effects on MAO-A in the gut**
  - **Rasagiline (Azilect®) - used in Parkinson's disease**

Available Antidepressants

Monoamine Oxidase Inhibitors (MAOIs)			
Drug	Brand Name	Initial Dose (mg/day)	Usual Dosage Range (mg/day)
Phenelzine	Nardil	15	30–90
Selegiline (transdermal)	Emsam	6	6–12
Tranylcypromine	Parnate	10	20–60

- **Although not specifically listed on BEER's List, use with caution due to potential Drug INX**

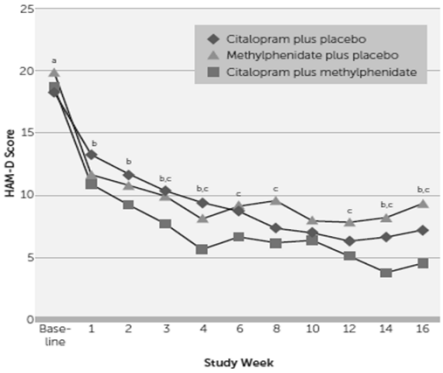
St. John's Wort

- **Active ingredient – hypericum**
- **Available as herbal supplement**
  - **Not regulated by the FDA in same way as typical OTC products**
  - **Manufacturers are not required to provide proof of safety and/or efficacy**
- **Significant drug interactions with commonly used medications – acts like a SSRI**
- **Should be administered under the guidance of a clinician trained in the treatment of depression and a single-source product should be used continuously from a reputable and trusted manufacturer**

Adjunct Therapies

- **Methylphenidate (Ritalin, others)**
  - **Used to elevate mood/increase activity levels in early disease.**
  - **Caution: stimulatory effects dangerous in cardiovascular disease**

FIGURE 2. Change in 24-Item Hamilton Depression Rating Scale (HAM-D) Score Over Time, by Treatment Condition, Among Patients Receiving Citalopram, Methylphenidate, or Their Combination



[a] Statistically significant difference between citalopram plus placebo and methylphenidate plus placebo, $p<0.05$.
[b] Statistically significant difference between citalopram plus placebo and citalopram plus methylphenidate, $p<0.05$.
[c] Statistically significant difference between methylphenidate plus placebo and citalopram plus methylphenidate, $p<0.05$.

Lavretsky H, et al. Citalopram, Methylphenidate, or Their Combination in Geriatric Depression: A Randomized, Double-Blind, Placebo-Controlled Trial. Am J Psychiatry 2015; 172:561–569; doi: 10.1176/appi.ajp.2014.14070889

Treatment Resistant Depression

- **Subset of Major Depressive Disorder not responsive to traditional and first-line therapeutic options**
  - **Inadequate response to at least 2 trials of antidepressant pharmacotherapy**
- **Pharmacological strategies**
  - **Lithium, triiodothyronine and second-generation antipsychotics**
  - **Switching antidepressant class**
- **Somatic therapies**
  - **Brain stimulation (electroconvulsive therapy, repetitive transcranial magnetic stimulation, magnetic seizure therapy and deep brain stimulation**
  - **Psychotherapeutic strategies**
- **Novel therapeutics**
  - **Ketamine, psilocybin, anti-inflammatories and other new directions**
- **SSRI antidepressant plus atypical antipsychotic commonly used**

Adverse Effects - SSRIs

- Selective Serotonin Reuptake Inhibitors
  - Fluoxetine, citalopram, sertraline, paroxetine, escitalopram, and fluvoxamine
- Low affinity for histaminergic, α_1-adrenergic, and muscarinic receptors
- Most common adverse effects:
  - Gastrointestinal symptoms (nausea, vomiting, and diarrhea)
  - Sexual dysfunction (both males and females)
  - Headache
  - Insomnia
- Infrequent but significant ADRs – hyponatremia and enhanced antiplatelet effects

Adverse Effects - SSRIs

- Fewer anticholinergic and cardiovascular adverse effects than TCAs
- Not usually associated with significant weight gain
- Discontinuation or withdrawal syndrome
  - Longer half-life of drug or active metabolite are less likely to have withdrawal syndrome
- Some may have increased anxiety symptoms or agitation early in treatment
- Drug interactions
  - Pharmacokinetic – CYP 450 inhibition – esp. paroxetine and fluoxetine
  - Pharmacodynamic - Serotonin Syndrome

Adverse Effects - SNRIs

- Serotonin-Norepinephrine Reuptake Inhibitors
- Venlafaxine & desvenlafaxine- dose related; similar to SSRIs
  - Nausea
  - Sexual dysfunction
  - Activation
  - Dose-related increase in diastolic blood pressure
    - Baseline blood pressure not a useful predictor
    - Monitor blood pressure regularly
    - Dosage reduction or discontinuation necessary with sustained hypertension
- Duloxetine –
  - Relatively well tolerated in short-term clinical trials; experience with long-term studies and in larger populations needed
  - Nausea, dry mouth, constipation, decreased appetite, insomnia, and increased sweating

Adverse Effects - Aminoketones

- Bupropion – Common adverse effects
  - Nausea, vomiting, tremor, insomnia, dry mouth, and skin reactions
  - Seizure - strongly dose-related
    - Predisposing factors - history of head trauma and CNS tumor
    - Contraindicated with eating disorders (bulimia and anorexia) due to electrolyte abnormalities and higher risk for seizure
    - Incidence of seizures is 0.4% at daily doses of 450 mg (the FDA-approved maximum dose) or less
  - Pro-adrenergic effects - activation or agitation in some patients

Adverse Effects - Triazolopyridines

- Minimal anticholinergic effects and 5-HT agonist side effects
- Orthostatic hypotension possible
- Trazodone - Common effects
  - Sedation, cognitive slowing, dizziness
  - Priapism - approximately 1 in 6,000 male patients. May require surgical intervention (1 in 23,000), and can cause permanent impotence
- Nefazodone - Common adverse effects
  - Light-headedness, dizziness, orthostatic hypotension, somnolence, dry mouth, nausea, asthenia (weakness)
  - Hepatic injury (black box warning) - avoid use with active liver disease or with elevated baseline serum transaminases
  - No reports of priapism in men; one case report of nefazodone-induced clitoral priapism

Adverse Effects - Mixed 5HT-α2 Agents

- Mirtazapine - common adverse effects
  - Somnolence, weight gain, dry mouth, and constipation
  - Somnolence and weight gain less common at higher doses (increased NE effects)
  - Used in low doses for appetite stimulation in elderly or other at risk populations

Adverse Effects - TCAs

- Most commonly occurring side effects are dose related
- Cholinergic blockade (anticholinergic effects)
  - Dry mouth, constipation, blurred vision, urinary retention, dizziness, tachycardia, memory impairment, and delirium (at higher doses)
  - Some tolerance develops
  - Impacts patient adherence, especially in the elderly and with long-term use
  - Consider total 'antiAch load'
- Orthostatic hypotension
  - Common, dose-related, problematic
  - Attributed to affinity for adrenergic receptors

Adverse Effects - TCAs

- Cardiac conduction delays
  - Induce heart block in patients with a preexisting conduction disorder
  - Severe arrhythmias with overdose
- Weight gain (↓ adherence)
- Sexual dysfunction (↓ adherence)
- Cholinergic rebound after abrupt withdrawal (high doses >300 mg/day)
  - Dizziness, nausea, diarrhea, insomnia, and restlessness

Adverse Effects - MAOIs

- Common adverse effects
  - Postural hypotension
    - More likely with phenelzine
  - Weight gain
  - Sexual side effects (decreased libido, anorgasmia)
  - Mild to moderately sedating (phenelzine)
  - Stimulating effect (tranylcypromine)
    - Insomnia, fever, myoclonic jerking, and brisk deep tendon reflexes

Adverse Effects - MAOIs

- Rare Hypertensive crisis
  - Potentially serious and life-threatening with concurrent use with certain foods high in tyramine or medications
  - Potential for cerebrovascular accident and death
- Symptoms
  - Occipital headache, stiff neck, nausea, vomiting, sweating, and sharply elevated blood pressure
- Patients MUST BE instructed to consult a healthcare professional before taking any over-the-counter medications, including non-FDA approved items sold as herbal/dietary supplements

Special Populations - Elderly Patients

- Overtreatment/overdosage common
  - Age-related PKin and PDyn factors not considered
- Undertreatment also an issue
  - Overly conservative approach with advanced age or concurrent medical problems
- SSRIs usually first-choice
- Avoid TCAs (sedative, anticholinergic, and cardiovascular-related side effects)
- Bupropion and venlafaxine often selected (milder anticholinergic and less frequent cardiovascular side effect)

Special Populations - Elderly Patients

- Many elderly inadequately treated
- Depression missed or mistaken for another disorder (e.g. dementia)
- Depressive symptoms less prominent than other symptoms (loss of appetite, cognitive impairment, sleeplessness, anergia, and loss of interest)
- Individuals ≥65 have the highest suicide rates than any other age group
  - Increased risk highest during first 30 days of treatment – risk persists throughout initial 6 months

Key Concepts – Depression

- Follow Treatment Guidelines
- Rule out medical causes of depression and drug-induced depression
- Treatment goal
  - Resolution of current symptoms (remission)
  - Prevention of further episodes (relapse or recurrence)
- Adverse effects might occur immediately; resolution of symptoms can take 2 to 4 weeks or longer.
- Adherence is essential for successful outcome

Teter CJ, Kando JC, Wells BG. Chapter 51. Major Depressive Disorder. In: Pharmacotherapy: A Pathophysiologic Approach, 9e. New York, NY: McGraw-Hill; 2014. http://accesspharmacy.mhmedical.com/content.aspx?bookid=689&Sectionid=45310502. Accessed February 04, 2015.

Key Concepts – Depression

- Antidepressants considered equally efficacious
  - Other factors guide selection (age, side effects, past response)
- Evaluating response
  - Target signs and symptoms
  - Quality-of-life issues (roles, social functioning, occupational function)
  - Tolerability
- Evaluating inadequate response
  - Adequate dose
  - Adequate duration
  - Medication adherence

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Case Questions

For the following case, answer the following questions:

- **Is the individual exhibiting symptoms of Delirium, Dementia? Depression?**
- **What Risk Factors are present for altered cognition and mood?**
- **What Initial Management "Pearls" would you suggest?**
- **What Future Management "Pearls" would you suggest?**

Case Study: "BLANCHE"

- **82 y/o widowed female living at home**
- **Mild memory loss, but still manages all ADLs and most IADLs with minimal assistance from daughter**
- **Found early this morning (before dawn) wandering barefoot in neighborhood in night clothes**
- **Is this Delirium, Dementia, or Senility?**
- **What questions do you ask?**

"BLANCHE" (cont'd)

- Only sister died last week – funeral was 3 days ago
- Has been sad and tearful all weekend in response to loss
- Increasing confusion during afternoon of funeral, struggling with memories and names at times
- Insomnia over past 3-4 nights

"BLANCHE" (cont'd)

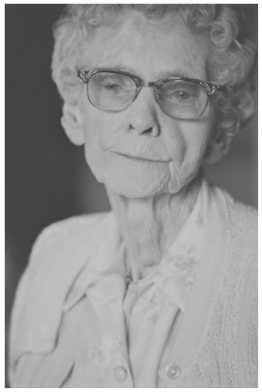
- Medications –
  - Rx: Hydrochlorothiazide 12.5 mg daily
    Detrol® LA 4 mg daily
    Paxil® CR 25 mg daily
  - OTC: APAP 325 mg PRN arthritis, multivitamin w/minerals, calcium + Vit. D, glucosamine sulfate/chondroitin
  - Other: Tylenol® PM – two tablets taken @ HS last night as recommended by daughter

Case Questions

- Is the individual exhibiting symptoms of Delirium, Dementia? Depression?
- What Risk Factors are present for altered cognition and mood?
- What Initial Management "Pearls" would you suggest?
- What Future Management "Pearls" would you suggest?

Case: CG

- CC: A 92 y/o female is admitted through the ER for mental status changes
- S: Granddaughter's husband states he found her standing in the living room wearing only pants when checking on her this morning
- PMH: one previous admission w/similar symptoms (CVA?), osteoarthritis, osteoporosis, constipation
- Meds: ASA 81 mg, clopidogril, APAP, calcium + vit. D, docusate



Case: CG (cont'd)

- Hospital Course:
  - PE – mumbling, confused, distracted, not responding to questions
  - Labs – UA suggestive of UTI
  - ECG – no acute changes
  - CG attempted to hit EKG technician after ECG leads abruptly removed from chest
  - Geropsych consulted for aggressive behavior
  - New orders:
    - Diphenhydramine 50 mg PO @ HS
    - Haloperidol 5 mg IM STAT, then 2 mg PO BID

Case: CG (cont'd)

- Discharge Orders
  - Admitted to Alzheimers Care Unit for further workup and convalescence
  - Diphenhydramine 50 mg PO @ HS
  - Haloperidol 2 mg PO BID
- Initial evaluation:
  - Elderly woman lying on bed in fetal position, unresponsive to questions except for occasional moan when moved

Case Questions

- Is the individual exhibiting symptoms of Delirium, Dementia? Depression?
- What Risk Factors are present for altered cognition and mood?
- What Initial Management "Pearls" would you suggest?
- What Future Management "Pearls" would you suggest?

Case: CG (cont'd)

- Initial New Orders
  - D/C diphenhydramine
  - Decrease haloperidol to 0.5 mg PO @ HS
- Status update:
  - 5 days post admission to ACU
    - Up ad lib walking in room and facility using wheeled walker w/seat
    - Interacting appropriately with staff and visitors
    - Holding conversation with use of bilateral hearing aids
    - No additional episodes of inappropriate behaviors
  - 20 days post admission to ACU
    - Moved to assisted living facility into efficiency apartment
    - Haloperidol D/C'd
    - Participating in all activities
    - Minimal interventions in ADLs necessary

Dementia, Delirium & Depression Summary

- Pharmacist role
  - Prevention and treatment through medication assessment
  - Assure appropriate treatment is implemented if needed
    - Drug
    - Dose
    - Duration
    - Drug Interactions

Therapy Update: Managing Dementia, Delirium, and Depression in Older Individuals

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