

# Management of Behavioral Symptoms in Alzheimer's Dementia

David Mansoor, MD

Associate Professor of Psychiatry

OHSU/PVAMC

July 2020

# Conflict of Interest Disclosure

- None.

OHIO STATE UNIVERSITY

# Overview

- Epidemiology
- Evaluation of neuropsychiatric symptoms
  - Identify target behaviors
  - Distinguish “agitation” from “aggression”
  - Mental status exam
- Environmental and medical causes
- Non-pharmacological interventions
- Medication management
  - Symptom oriented approach

# Epidemiology

- Dementias can be categorized by possible etiology
  - Alzheimer's dementia
  - Vascular dementia
  - Dementia with Lewy bodies
  - Frontotemporal lobar degeneration
  - Traumatic brain injury
  - Substance induced
  - Parkinson's disease
  - Etc.

# Epidemiology

- Nomenclature using DSM 5
  - “Dementia” replaced with “major neurocognitive disorder”
    - Prompted to specify the etiology
      - Major NCD due to Alzheimer’s disease
      - Major NCD with Lewy Bodies
      - Major vascular NCD
      - Major frontotemporal NCD
- I will be using the terms “dementia” and “neurocognitive disorder” interchangeably

# Epidemiology

- Loss in intellectual abilities
- Impairment in judgment
- Loss of executive function
- Personality changes
- Behavioral changes -> neuropsychiatric symptoms

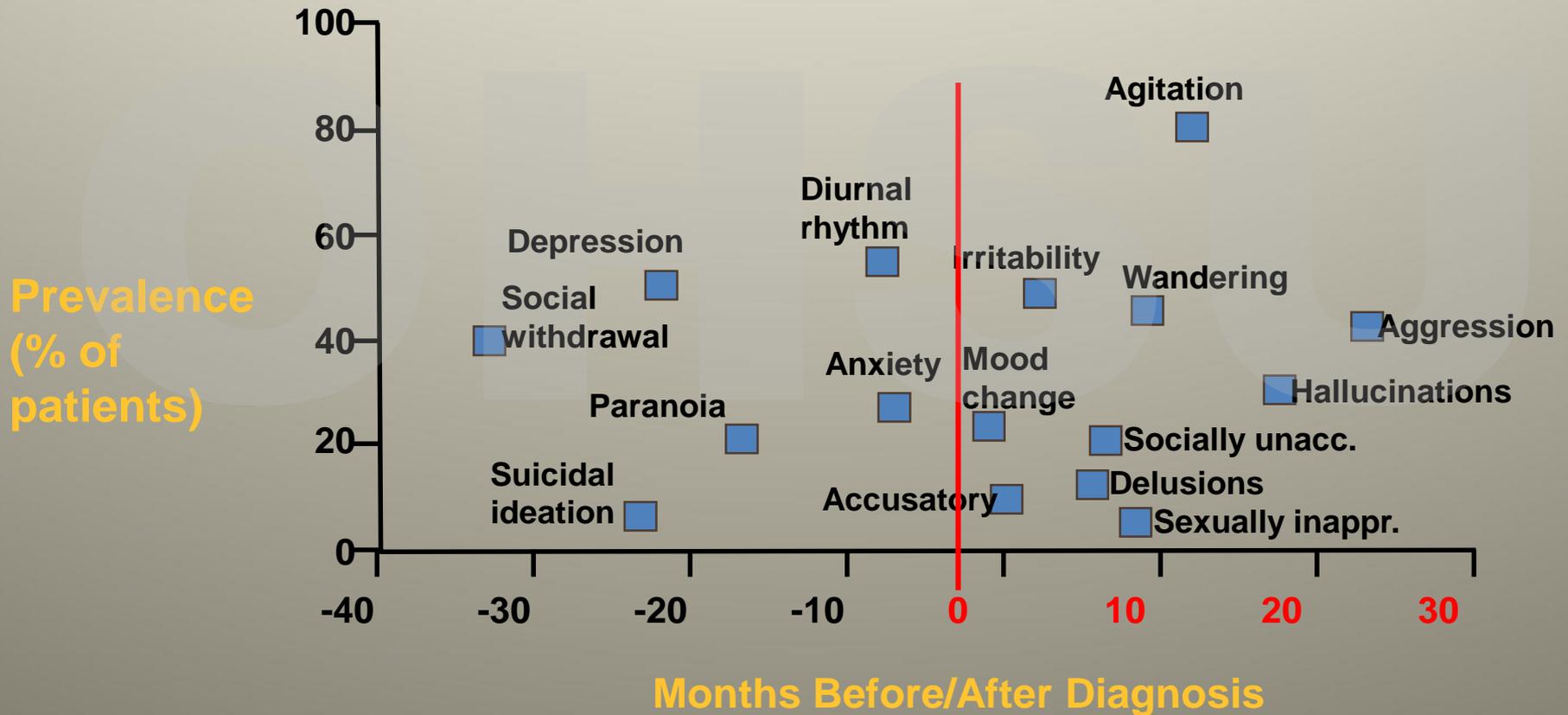
# Epidemiology: Neuropsychiatric Symptoms

- Common – a central component of dementia
  - Affect up to 80% of persons with dementia
- Morbid
  - Greater impairments in IADLs, more rapid rate of cognitive decline, earlier institutional decline, greater rate of caregiver depression
- Classifiable
- Treatable

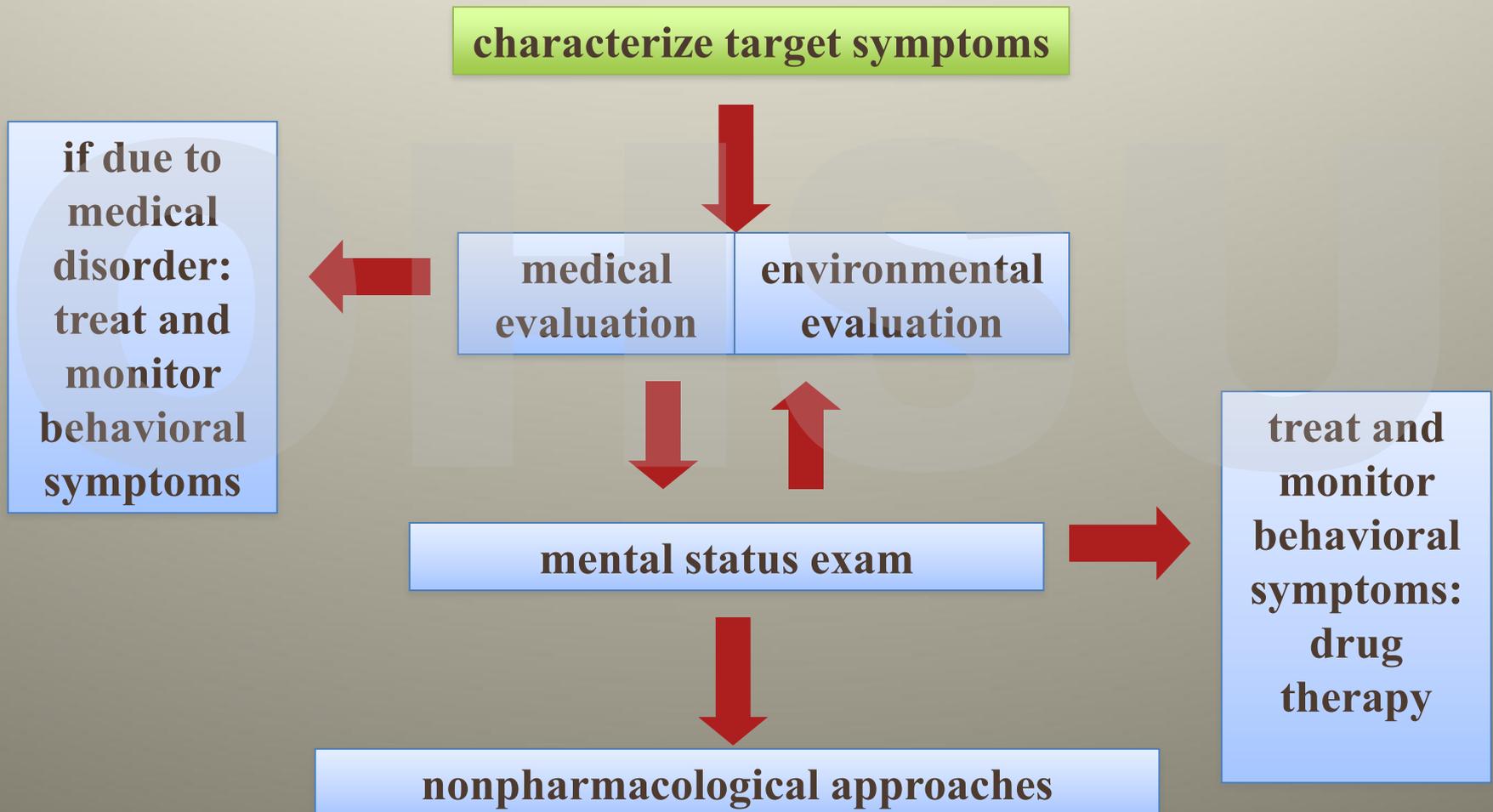
# Epidemiology: Prevalence of Symptoms in Dementia

<b>NPI Item</b>	<b>Dementia (n=329) %</b>	<b>No Dementia (n=673) %</b>
Apathy	27.4	3.1
Depression	23.7	7.0
Agitation/aggression	23.7	2.8
Irritability	20.4	4.5
Delusions	18.5	2.4
Anxiety	17.0	5.6
Aberrant motor behavior	14.3	0.4
Hallucinations	13.7	0.6
Disinhibition	9.1	0.9
Elation	0.9	0.3

# Peak Frequency of Behavioral Symptoms as Alzheimer's Disease Progresses



# General Approach to Behavioral Complications of Dementia



# Target Symptoms

- Before any intervention is initiated, observation and documentation to measure the nature, severity, and frequency of the symptoms
- Details are critical for directing care
- Selection of an intervention depends on the targeted behavioral symptom

# Target Symptoms: Case

- You are on call and receive a page from a care facility,
  - Your patient is an 82-year old patient with advanced Alzheimer’s disease who has been at an adult foster home for 2 years
  - “He is sundowning. We need something to calm him down.”
    - “he is agitated”



# Target Symptoms: Case

- Define target behaviors
- A precise description can assist with identifying the underlying cause and selection of effective interventions
- “Agitation” is commonly used
  - It is nonspecific
  - It is not a diagnostic term
  - No universal definition
  - Often subjectively assigned by an observer depending on whether or not the behavior seems appropriate
  - Often associated with discomfort

# Target Symptoms: Case

- Agitation includes
  - General restlessness
  - Pacing
  - Complaining
  - Repeating sentences
  - Cursing
  - Kicking
  - Hitting
  - Name calling

# Target Symptoms

- Aggressive
  - Physical
  - Verbal
- Nonaggressive
  - Physical
  - Verbal

# Target Symptoms

- Physical aggression: hostile acts directed toward others, self, or objects
  - Hitting, kicking, biting, grabbing, scratching
  - *Tend to occur in later stages*
  - Often during times of close contact
  - More common in men than women

# Target Symptoms

- Verbal aggression: temper outbursts, making strange noises, screaming, cursing, threatening, accusations, name calling

# Target Symptoms

- Physical nonaggression: repetitive activities
  - Wandering, pacing, checking, disrobing, repeating gestures or movements
- Verbal nonaggression: complaining, repeating words and sentences, constant talk, calling out

# Target Symptoms

- Helps to understand etiology
  - Wandering: looking for home? bathroom? anxiety? akathisia?
  - Verbal repetition: sensory deprivation? confusion? hunger? thirst?
  - Aggression: psychosis? fear? pain?

# Target Symptoms: Case

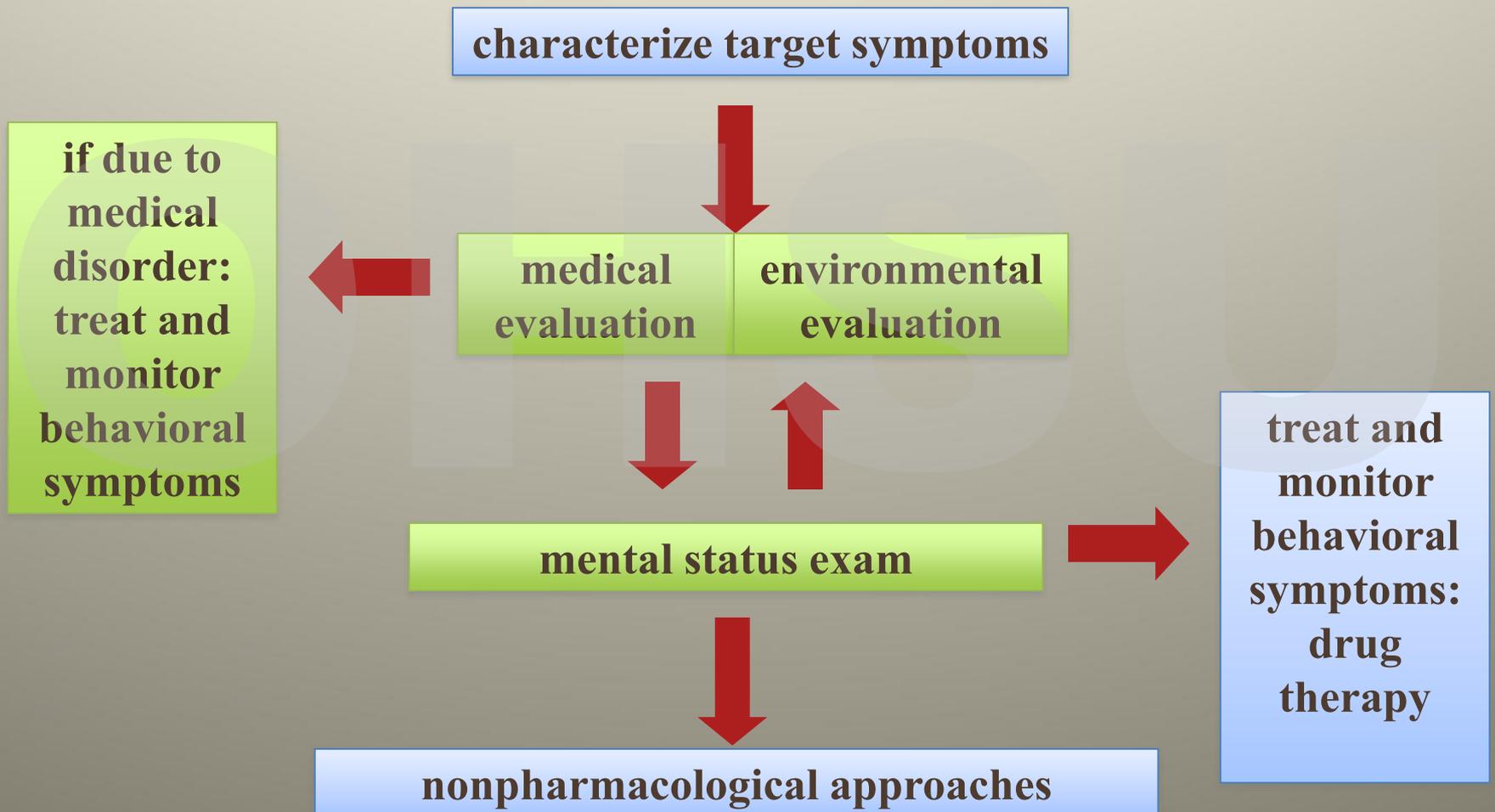
- At a clinic visit, a caregiver says your patient Mrs Y is having “hallucinations”
- She is a 75-year old with moderate Alzheimer’s disease who lives at home



# Target Symptoms: Case

- Define the target behavior / symptom
- Hallucinations?
  - Auditory?
  - Visual?
- Delusions?
  - Paranoid?
    - Spouse having an affair; stealing; others in the house
  - Misidentification? (Capgras delusion)

# General Approach to Behavioral Complications of Dementia



# Evaluation: Mental Status Exam

- General appearance:
  - Grooming? Weight? In pain? Level of consciousness?
- Behavior
- Speech
  - Quantity? Smooth/effortless or halting?
- Language
  - Word finding difficulty → General use-phrases (“that thing,” “you know what I mean”) with comprehension difficulty
- Mood
  - “How are your spirits today?”
- Affect
  - Anxious? Depressed?

# Evaluation: Mental Status Exam

- Thought process
  - Linear? Circumlocution? Disorganized?
- Thought content
  - Delusional? Hallucinations?
- Insight
  - Anosognosia
- Cognition
  - 30-pt mental status exam
    - How far off from baseline?
    - Tests of attention can help to distinguish delirium from dementia

# Evaluation – Medical

- Discomfort / Pain
  - Musculoskeletal
  - Constipation
  - Urinary retention
  - Hunger, thirst
- Infection
- Medications
  - Benzodiazepines, opiates, anticholinergics, antihistamines

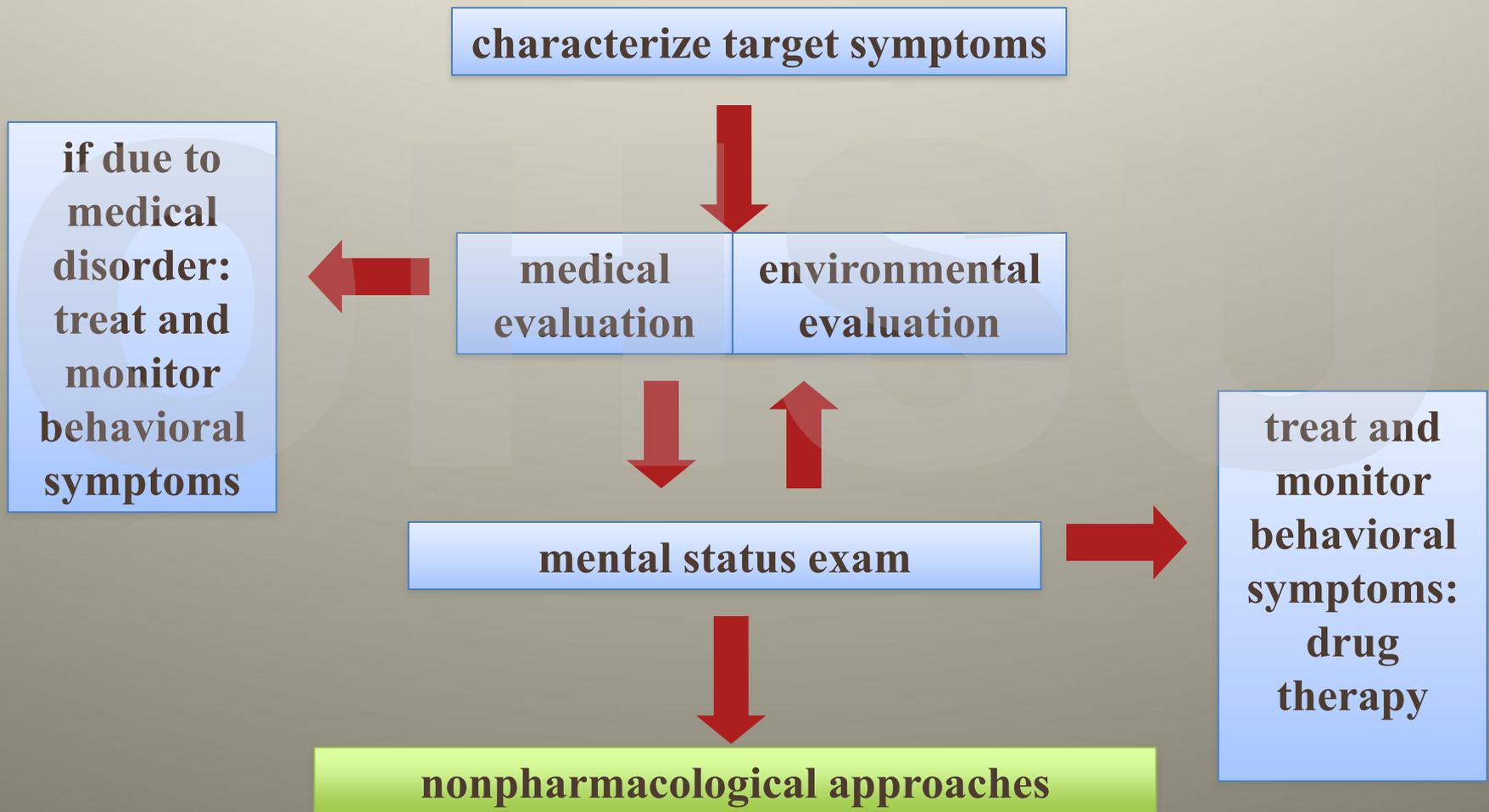
# Evaluation – Medical

- Basic labs as indicated
  - CBC, chemistry panel, TSH, b12
  - Urinalysis for urinary tract symptoms
- Imaging only as indicated
  - New neurologic finding
  - Recent fall with mental status change, headache, neurologic findings

# Evaluation - Environment

- Environment
  - Overstimulating?
    - TV, telephone, visitors, mirrors, pictures...
  - Understimulating?
    - Dark, quiet, reduced sensory input
  - Unfamiliar
    - Transition can be disruptive

# General Approach to Behavioral Complications of Dementia



# Non-Pharmacological Approach

- Develop a structured daily routine
- Offer daytime recreational therapy
- Increase physical activity during the day and avoid napping
- Create a quiet and comfortable sleep environment
- Limit evening fluid intake, empty bladder
- Bright light during the day and darkness at night
- Avoid caffeine, alcohol, nicotine

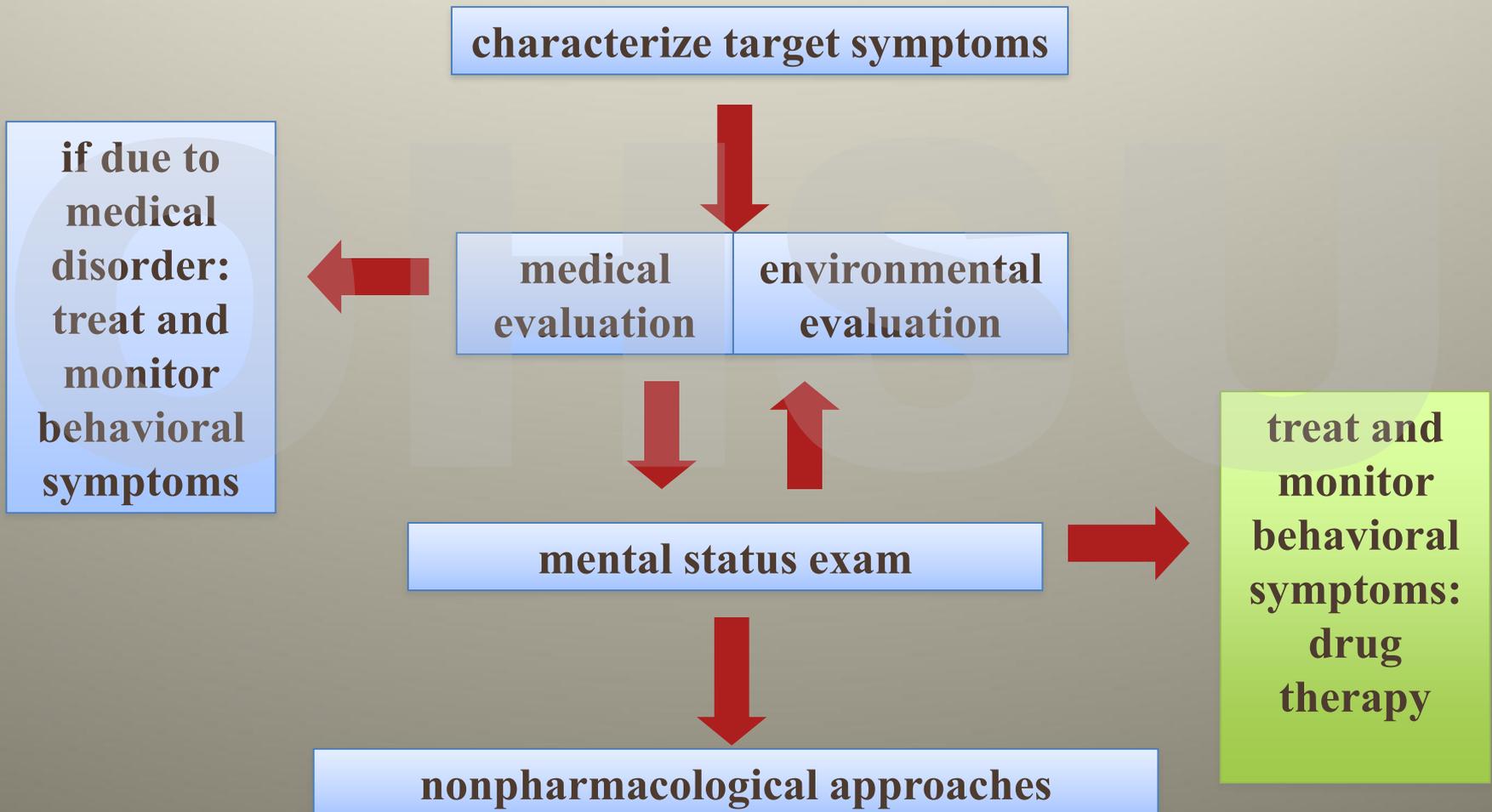
# Non-pharmacological Approach

- Bathing: make bathroom safe, comfortable room and water temp, don't rush, wash hair last, towel bath
- Dressing: limit choices, prepare clothing, large clothing and soft stretchy fabric, Velcro shoes
- Eating: maintain regular mealtime, avoid distraction, check food temperature, finger foods, sweeten foods,

# Non-pharmacological Approach

- Wandering: provide adequate daily physical activity, create safe wandering paths, remove reminders of leaving (coats, umbrellas), alarms or bells at door exits, ID bracelet
- Incontinence: schedule voiding, nonverbal cues (pacing), put signs at the bathroom door, clear obstacles
- Delusions: avoid challenging

# General Approach to Behavioral Complications of Dementia



# Considerations

- There are no FDA approved medications for treating behavioral symptoms due to dementia
- There is no magic bullet
- Typically need a combination of behavioral intervention and pharmacotherapy

# Considerations

- When using a medication, do so judiciously, in the lowest effective doses, and for the shortest period of time necessary
  - Start low and go slow (but go!)
- Age related physiologic change -> more susceptible to side effects

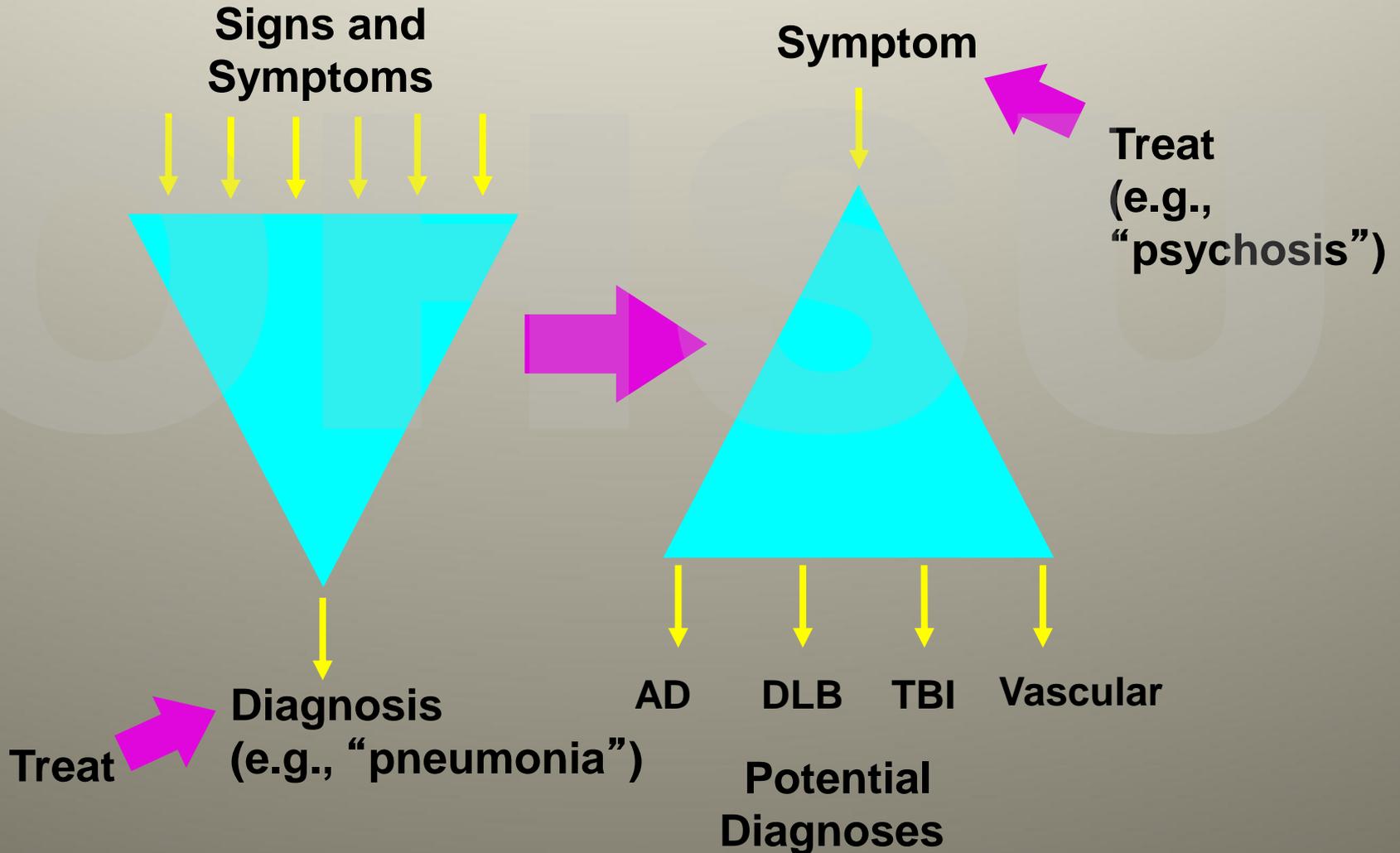
# Considerations

- Ineffective medications should be stopped
- Consideration should be given to periodic trial dose reductions of effective medications to learn whether treatment is still necessary

# SYMPTOM ORIENTED APPROACH

# Symptom Oriented Approach

Traditional Approach    New Approach



# Symptom Oriented Approach to Treatment

- Define the target behaviors
- Look for a pattern in the patient's behavior which is analogous to that typically seen in a "drug responsive" psychiatric syndrome
- Psychotic – overly suspicious, angry when approached, delusional
- Depressive – irritable, sad, vegetative, withdrawn
- Manic – impulsive, accelerated, hypersexual, labile affect
- Anxious – worry, restless, somatic concerns

# Symptom Oriented Approach to Treatment

- Match the target symptom to the drug class

Behavioral disturbance	Drug to consider
Depressive Spectrum	Antidepressant
Psychotic Spectrum	Antipsychotic
Manic	Mood Stabilizer
Anxiety Spectrum	SSRI

# Symptom Oriented Approach to Treatment

Behavioral disturbance	Drug to consider
Aggression / Anger Mild / Acute	Trazodone
Aggression / Anger Mild / Longterm	SSRI, Depakote, CI
Aggression / Anger Severe / Acute	Antipsychotic

# TREATMENT BY DRUG CLASS



# Considerations

- Multiple classes of psychotropic medication have demonstrated efficacy in treating agitation
  - Antidepressants
  - Mood stabilizers
  - Cholinesterase inhibitors
  - Antipsychotics

# Antidepressants

(for Depression and Agitation)

# Antidepressants - Agitation

- Often used because well tolerated and have few serious side effects
- Few studies of antidepressants for the treatment of agitation and psychosis in dementia
- Most studies have been small, did not control for depressive symptoms, varying results

# Antidepressants - Agitation

- Cochrane Review 2011:
  - The SSRIs sertraline and citalopram were associated with a reduction in symptoms of agitation when compared to placebo in two studies
  - Both SSRIs and trazodone appear to be tolerated reasonably well when compared to placebo, typical antipsychotics and atypical antipsychotic
- “Antidepressants such as citalopram, sertraline, and trazodone **may improve symptoms** of agitation and psychosis for some individuals with dementia and given that the tolerability and safety of these medications appears to be similar to placebo and certain antipsychotics, these medications **may be considered** as a potential treatment for these symptoms”

# Antidepressants - Agitation

- APA Practice Guidelines (2007)
  - “a therapeutic trial of trazodone, buspirone, or an SSRI may be appropriate for some nonpsychotic but agitated patients, especially those with relatively mild symptoms or those who are intolerant of or unresponsive to antipsychotics”

# Antidepressants - Depression

- APA Practice Guidelines (2007)
  - “Although evidence for antidepressant efficacy in patients with dementia and depression is mixed, clinical consensus supports a trial of an antidepressant to treat clinically significant, persistent depressed mood. The choice among agents is based on the side-effect profile of specific medications and the characteristics of the individual patient. SSRIs may be preferred because they appear to be better tolerated than other antidepressants. Bupropion, venlafaxine, and mirtazapine may also be effective.”
- American Academy of Neurology - “SSRIs should be considered to treat depression”

# Antidepressants

- Consider for depression or agitation driven by underlying depression
- Avoid older tricyclics (amitriptyline, imipramine, etc)
- Start low and go slow
  - Escitalopram
  - Sertraline
  - Mirtazapine
  - Trazodone PRN or scheduled

# Antidepressants – Side Effects

- Constipation
- Diarrhea
- Dizziness
- Dry mouth
- Falls
- Nervousness
- Headache
- Nausea
- Tremor
- Decreased libido
- Gait instability
- Fatigue

# Cognitive Enhancers: Cholinesterase Inhibitors and Memantine

# Cholinesterase Inhibitors

- Increase Ach in in the synaptic cleft
- Galantamine, Rivastigmine, Donepezil
  - 2009 Systematic Review: mixed <sup>1</sup>
  - Generally well tolerated, benefit cognition and function, worth trying if symptoms are mild or if risks of other medications are high
  - **Dementia with Lewy bodies**
  - Frontotemporal dementia <sup>2</sup>

1. Rodda J. Are Cholinesterase Inhibitors Effective in the Management of Behavioral and Psychological Symptoms of Dementia in Alzheimer's Disease? *International Psychogeriatrics*. 2009.

2. Mendez MF, Shapira JS: Preliminary findings: behavioral worsening on donepezil in patients with frontotemporal dementia. *Am J Geriatr Psychiatry* 2007; 15:84—87

# Cholinesterase Inhibitors

- Adverse effects
  - Bradycardia
  - AV Block
  - Syncope
  - Seizures
  - Peptic ulcer
  - Hallucinations
  - Nausea
  - Vomiting
  - Diarrhea
  - Abdominal pain
  - Confusion
  - Sedation
- Drug interactions
  - Anticholinergics
  - Bupropion
  - Beta blockers
  - NSAIDs

# Memantine

- Memantine (Namenda)
  - Binds NMDA receptor, inhibits influx of  $\text{Ca}^{2+}$  ions, reduces glutamate induced neuronal toxicity
  - Indicated for moderate to severe Alzheimer's
  - Literature is also mixed and limited
    - Most studies recruited patients for the purpose of testing cognition, not behavioral symptoms
  - Also generally well tolerated, with cognitive and functional benefit in patients with moderate to severe dementia

# Mood Stabilizers

# Valproic Acid

- Anecdotal reports abound along with positive open label studies
- Effective in a broad range of psychiatric conditions characterized by agitation
- Consider for aggressive / impulsive behavior in the absence of psychotic symptoms or mood lability
- Sedation, GI upset, tremor, thrombocytopenia

# Antipsychotics

# Antipsychotics

- Traditional mainstay for reducing agitation for decades
- May increase mortality and stroke
  - 1.6 x increase in mortality compared with placebo (4.5% vs 2.6%)
- Benefits often still outweigh the risks in patients when treatment of hallucinations and delusions are critical
  - Individual risk/benefit analysis

# Antipsychotics

- Typical Antipsychotics, Haloperidol
  - Cochrane Review updated in 2010
    - Haloperidol was useful in the control of aggression/hostility/suspiciousness
    - “There is little evidence to support a benefit of haloperidol on manifestations of agitation other than **aggression**”
    - Adverse effects more common than placebo
- Atypical Antipsychotics
  - 2006 Cochrane Review of placebo-controlled trials
    - Risperidone 1-2mg and olanzapine 5-10mg improved aggression compared to placebo
    - Risperidone improved **psychosis** relative to placebo

# Antipsychotics

- Side effects: EPS, orthostasis, akathisia, sedation, metabolic, cerebrovascular events, upper respiratory tract infection, cardiac events
- Cumulative incidence of tardive dyskinesia 26%, 52%, and 60% after 1, 2, and 3 years<sup>1</sup>
  - Typical neuroleptics
- **Avoid in dementia with Lewy bodies!!!**

1. Jeste DV, Caligiuri MP, Paulsen JS, et al. Risk of tardive dyskinesia in older patients. A prospective longitudinal study of 266 outpatients. *Arch Gen Psychiatry.* 1995;52: 756-765.

# Other: Benzodiazepines and Diphenhydramine

# Benzodiazepines and Diphenhydramine

- Benzodiazepines
  - Minimal data supporting efficacy
  - Sedation, falls, cognitive impairment
  - Should be avoided
- Diphenhydramine
  - Anticholinergic
  - Avoid
  - **May worsen cognition and behaviors**

# Hypnotics for Sleep

# Hypnotics

- Try to implement non-pharm interventions
- Consider a trial of trazodone
- Consider a trial of mirtazapine if there are coexisting mood or anxiety symptoms
- Melatonin – literature is mixed
  - Studies have looked at doses 2mg-10mg
  - Generally well tolerated
- Do not use antipsychotics solely as hypnotics
- Do not use hydroxyzine, Benadryl, or benzos!

# Summary

# “Pearls”

- Use data to formulate a hypothesis of cause of behavior
- Start with nonpharmacological approaches
- Reserve pharmacotherapy for behaviors that are severe, persistent, and/or resistant to nonpharmacological treatments

# “Pearls”

- If monotherapy fails, use judicious combination of medications (eg, antidepressants with antipsychotics or with mood stabilizers)

# “Pearls”

- If lots of medications do not help, start discontinuing medications
  - Can they be any worse off medications?
  - Are they experiencing interactive side effects?

# “Pearls”

- Less-severe behaviors with limited consequences of harm to individual or caregiver are appropriate for nonpharmacologic therapy, not antipsychotic therapy
- More severe or “high risk” behaviors such as frightening hallucinations, delusions or hitting may require addition of antipsychotic trial

# Question

- You are treating a patient with very distressing paranoia due to advanced Alzheimer's disease. This has led to caregiver mistrust, refusal of care, and physically aggressive behavior. You plan to start an antipsychotic medication. In discussing the risks and benefits of antipsychotics in older adults with behavioral symptoms associated with dementia, which of the following is accurate:
  - A. A black box warning exists because of the increased risk of death
  - B. Antipsychotic medications can help to treat parkinsonism symptoms, if present
  - C. Antipsychotic medications slow progression of cognitive decline in patients with Alzheimer's disease
  - D. Antipsychotics lower the risk of stroke

# Question

- You are consulting on a 72-year old woman who suffers from dementia with Lewy bodies. She has distressing visual hallucinations and has been acting on the delusion that people are in the room trying to harm her. Which of the following medications should be avoided because of the risk of worsening parkinsonism:
  - A. Haloperidol (first generation anti-psychotic)
  - B. Donepezil (cholinesterase inhibitor)
  - C. Trazodone (anti-depressant)
  - D. Memantine (NMDA receptor antagonist)

# Question

- Your patient is an 82-year old woman with moderate stage Alzheimer's disease. For the past 3 weeks she has been suspicious of her caregivers and having difficulty sleeping. Which of the following medications are FDA approved for treating behavioral symptoms in Alzheimer's disease:
  - A. Antipsychotics
  - B. Antidepressants
  - C Cholinesterase inhibitors
  - D. No medications are FDA approved for treating behavioral symptoms in Alzheimer's disease

# Question

- Your patient is an 80-year old with moderate Alzheimer's disease. He presents with symptoms of apathy and low motivation. Neuropsychiatric symptoms are seen in approximately what percentage of patients with dementia:
  - A. 0-10%
  - B. 10-20%
  - C. 30-50%
  - D. 60-80%

# Question

- You are evaluating a 75-year old patient with early Alzheimer's disease. He describes a several month history of low mood and sleep disturbance. Which of the following symptoms would support a diagnosis of major depression:
  - A. Visual hallucinations
  - B. Skin picking
  - C. Decreased appetite with weight loss
  - D. Disorientation

**The End**

email me: [mansoord@ohsu.edu](mailto:mansoord@ohsu.edu)