Management of Behavioral Symptoms in Dementia

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Conflict of Interest Disclosure

- None

Overview

- Epidemiology
- Evaluation of neuropsychiatric symptoms
  - Identify target behaviors
- *Environmental and medical causes*
- *Non-pharmacological interventions*
- Medication management
  - Symptom oriented approach

Epidemiology

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

- Impairment in learning and memory
- Attentional impairment
- Loss of executive function
- Impairment in language
- Perceptual motor dysfunction
- Behavioral changes -> neuropsychiatric symptoms

Epidemiology: Neuropsychiatric Symptoms

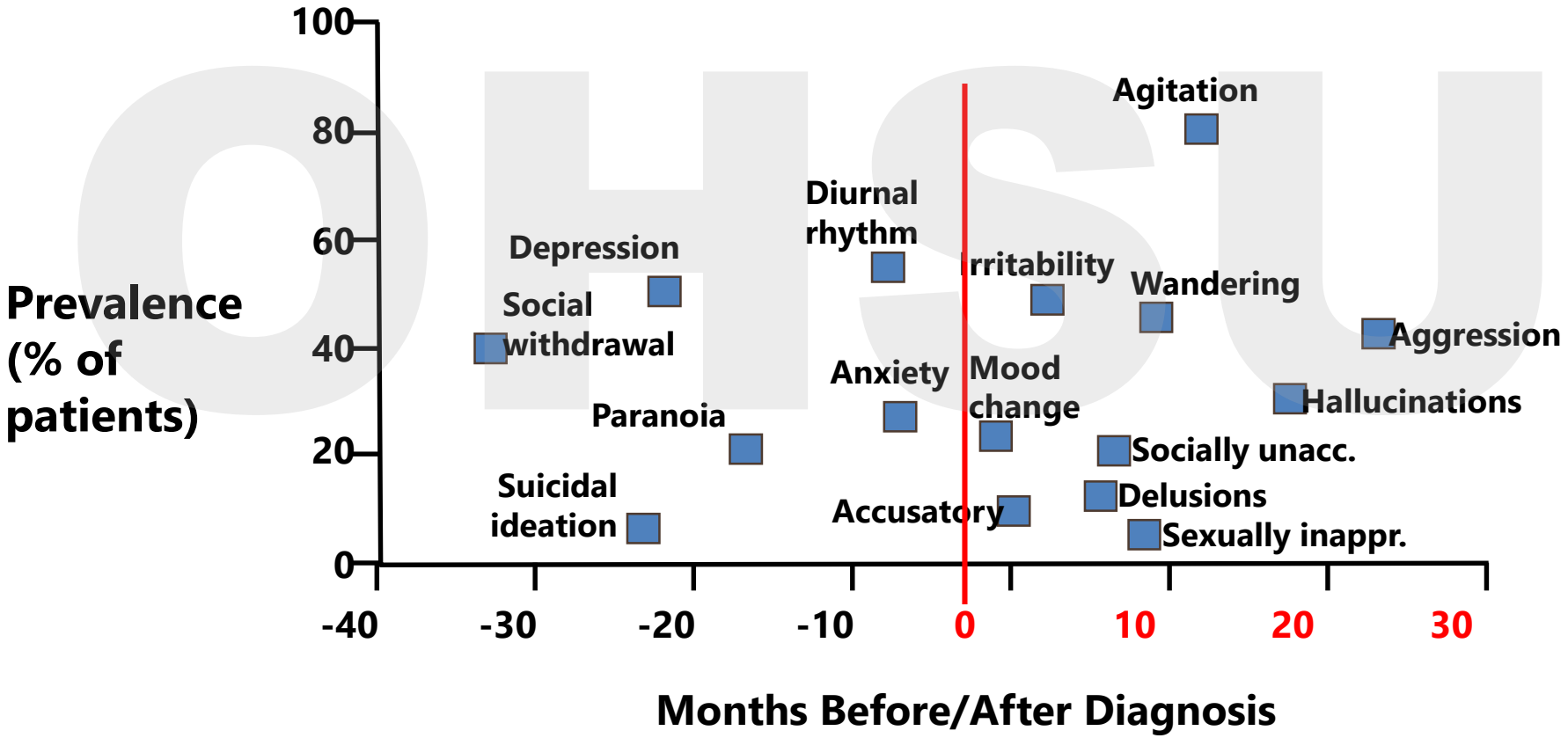
- Common – a central component of dementia
  - Affect up to 80% of persons with dementia
- Morbid
  - Greater impairments in IADLs, more rapid rate of cognitive decline, earlier institutionalization, greater rate of caregiver depression
- Classifiable
- Treatable

Epidemiology: Prevalence of Symptoms in Dementia

NPI Item	Dementia (n=329) %	No Dementia (n=673) %
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

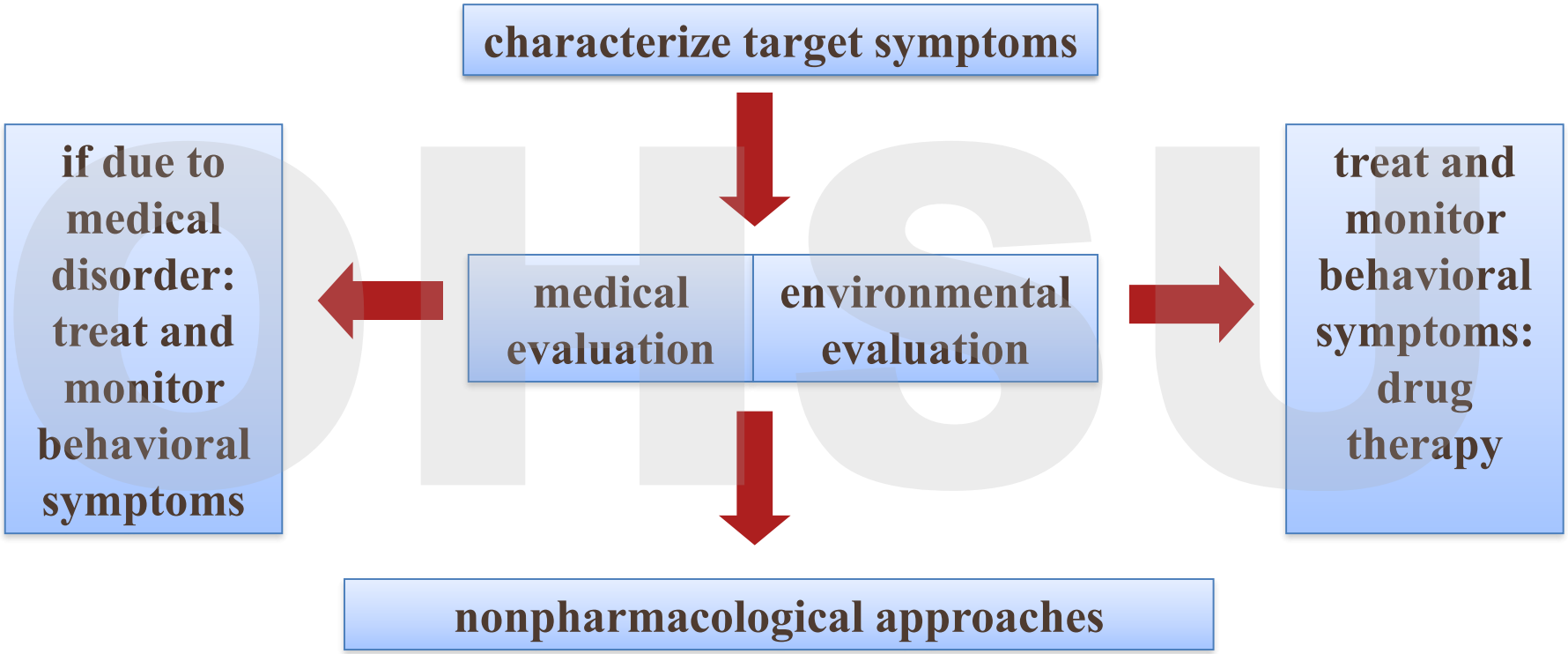
Lyketsos CG et al. *Am J Psychiatry*. 2000;157:708-714. American Psychiatric Association.

Peak Frequency of Behavioral Symptoms as Alzheimer's Disease Progresses

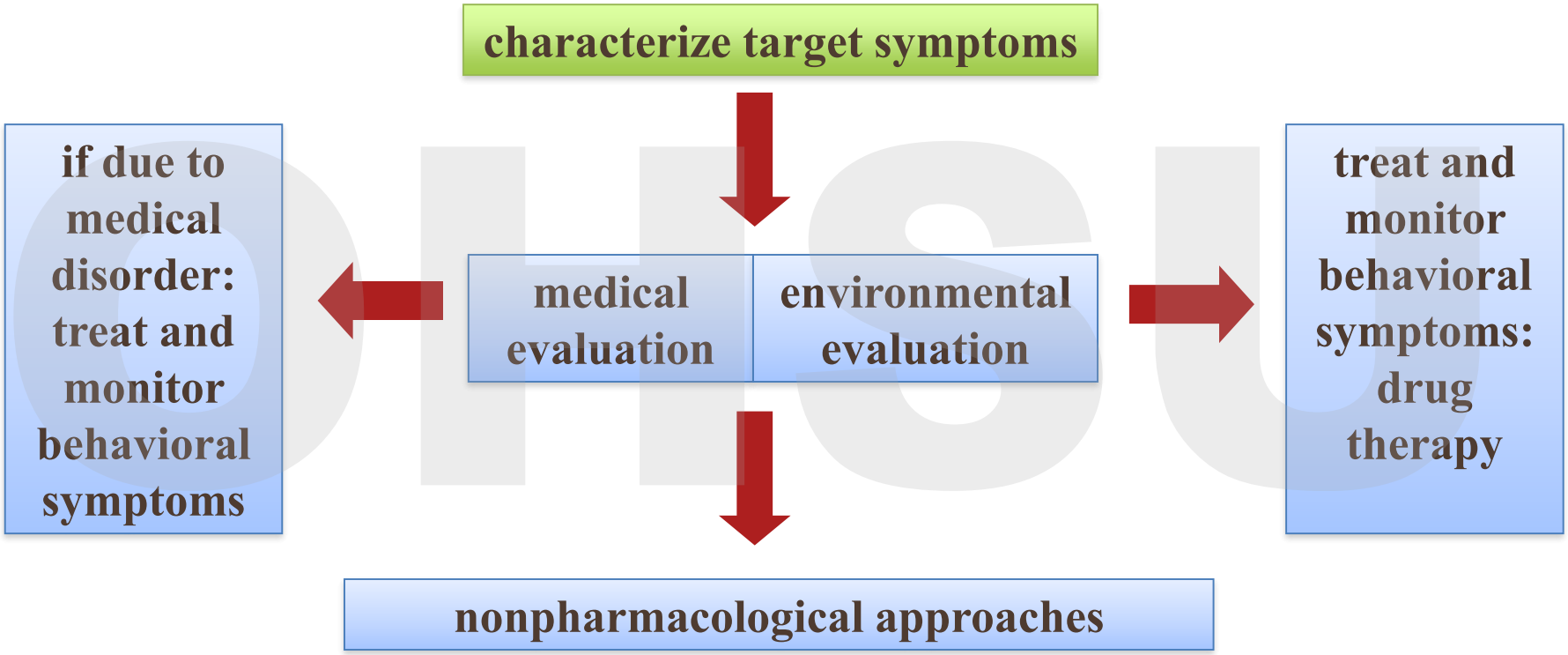


Jost BC, Grossberg GT. J Am Geriatr Soc. 1996;44:1078-1081.

General Approach to Behavioral Complications of Dementia



General Approach to Behavioral Complications of Dementia



Target Symptoms

- Before any intervention it is important to understand the nature, severity, and frequency of the symptoms
  - Details are critical for directing care
- Selection of an intervention depends on the targeted behavioral symptom AND the cause

Target Symptoms: Case 1

- You are on call and receive a page from a care facility,
  - 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 1

- "Agitation" is commonly used
  - It is nonspecific
  - It is not a diagnostic term
  - No universal definition
  - Variably used: typically assigned by an observer depending on whether *they think* the behavior seems appropriate
  - Doesn't help you to establish cause / severity / safety
- A more precise description can assist with identifying the underlying cause and selection of effective interventions
- Define target behavior

Target Symptoms

- Aggressive (hostile/violent)
  - Physical
  - Verbal
- Nonaggressive
  - Physical
  - Verbal

Cohen Mansfield Agitation Inventory

Target Symptoms

- **Physical aggression**: hostile acts directed toward others, self, or objects
  - Hitting, kicking, biting, grabbing, scratching, spitting, hurting self or others, destroying property, physical sexual advances
  - Tend to occur in later stages
  - May be associated with psychosis
  - Often during times of close contact

Target Symptoms

- **Verbal aggression**: temper outbursts, making strange noises, screaming, cursing, threatening, accusing, name calling, verbal sexual advances

Target Symptoms

- **Physical nonaggression**
  - Repetitive mannerisms, general restlessness, wandering, pacing, disrobing, trying to get to a different place, hoarding, refusing care
- **Verbal nonaggression**
  - Complaining, repeating words and sentences, constant talking, strange noises, calling out

Target Symptoms

- Rating scales can be very helpful, and are recommended by the APA
  - Cohen Mansfield Agitation Inventory
    - 29-item scale
    - Caregiver rates frequency of behavior over prior 2 weeks
  - Neuropsychiatric Inventory Questionnaire
    - 12-item scale
    - Caregiver rates presence/absence of behavior, severity (mild/moderate/severe), level of distress over prior month

Target Symptoms

- Helps to understand etiology
  - *Wandering*: looking for home? looking for bathroom? anxious? akathisia? understimulated?
  - *Verbal repetition*: sensory deprivation? confusion? hunger? thirst?
  - *Aggression:* psychosis (delusion, hallucination)? fearful? in pain?

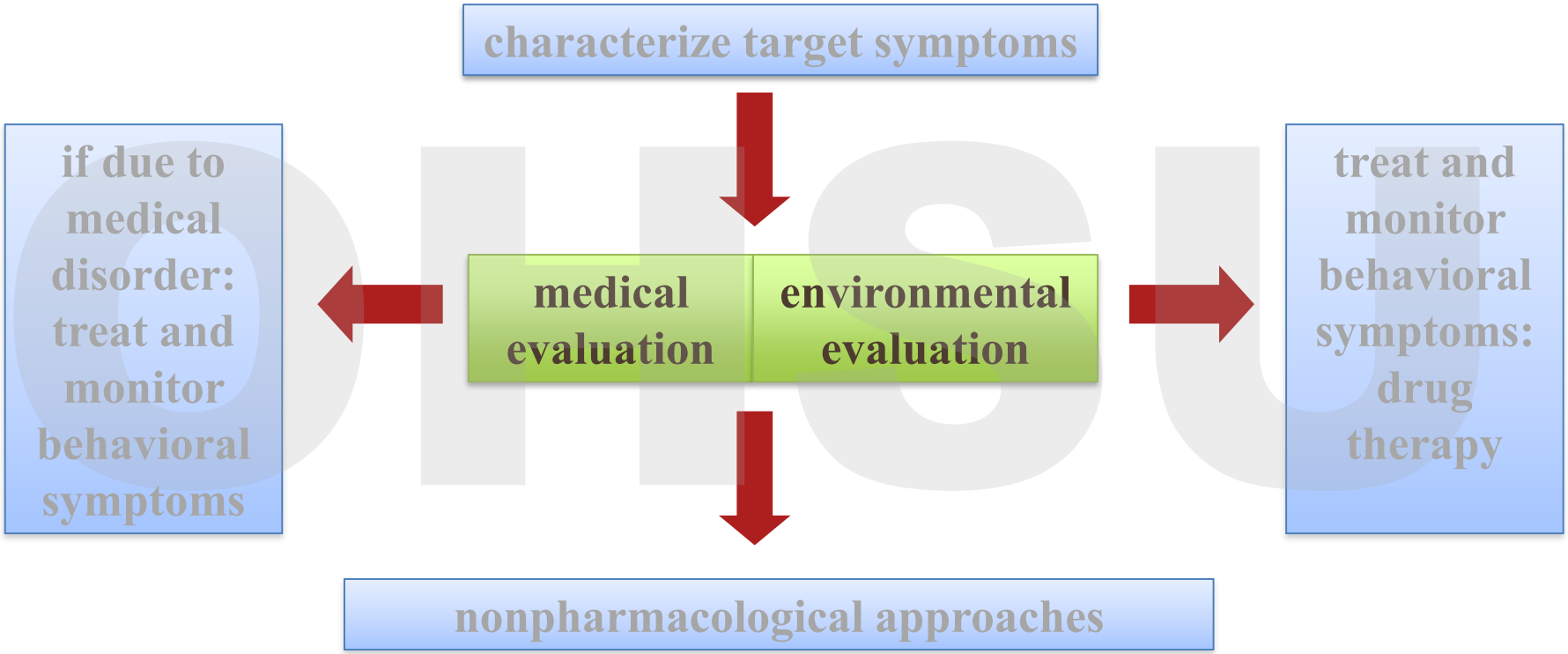
Target Symptoms: Case 2

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

Target Symptoms: Case 2

- Define the target behavior / symptom
  - "what do you mean by hallucination?"
- Hallucinations?
  - Auditory?
  - Visual?
- Delusions?
  - Paranoid?
    - Spouse having an affair; stealing; others in the house
  - Misidentification? (eg, spouse isn't their spouse)

General Approach to Behavioral Complications of Dementia



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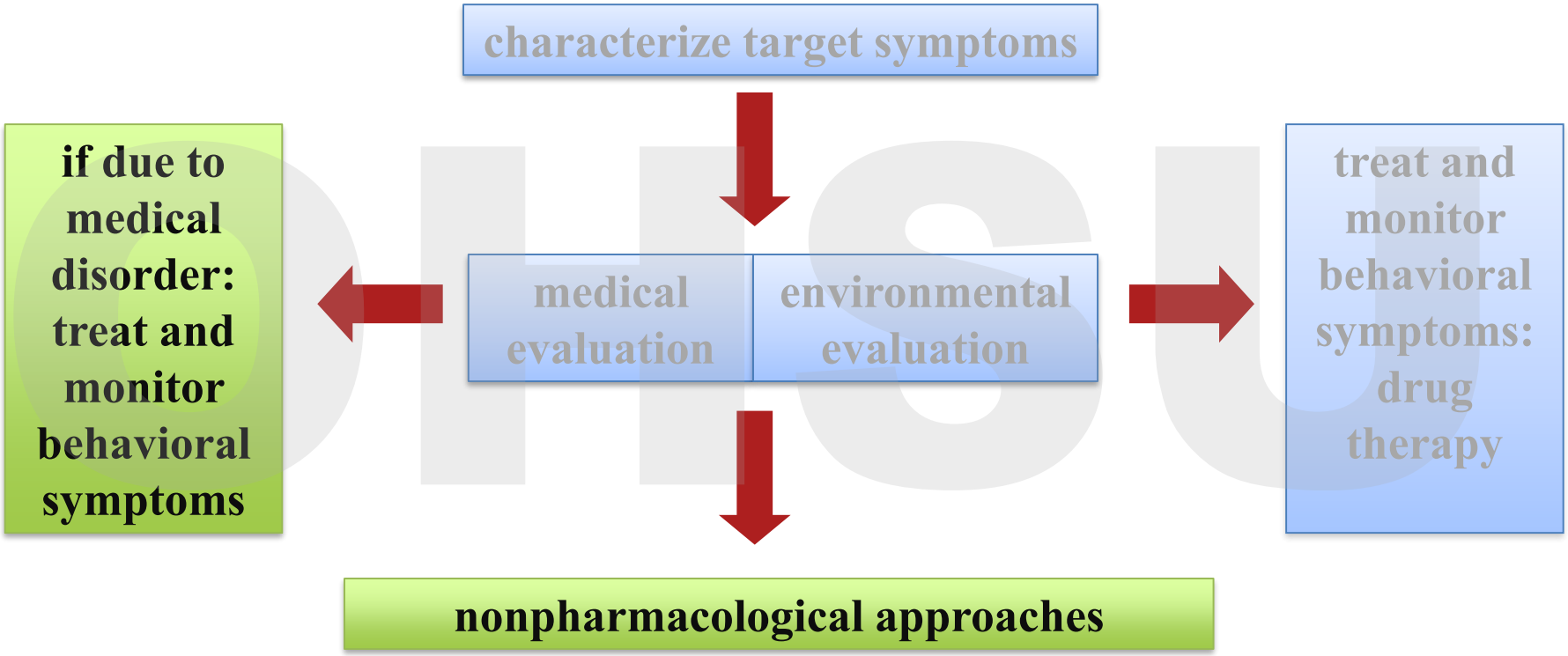

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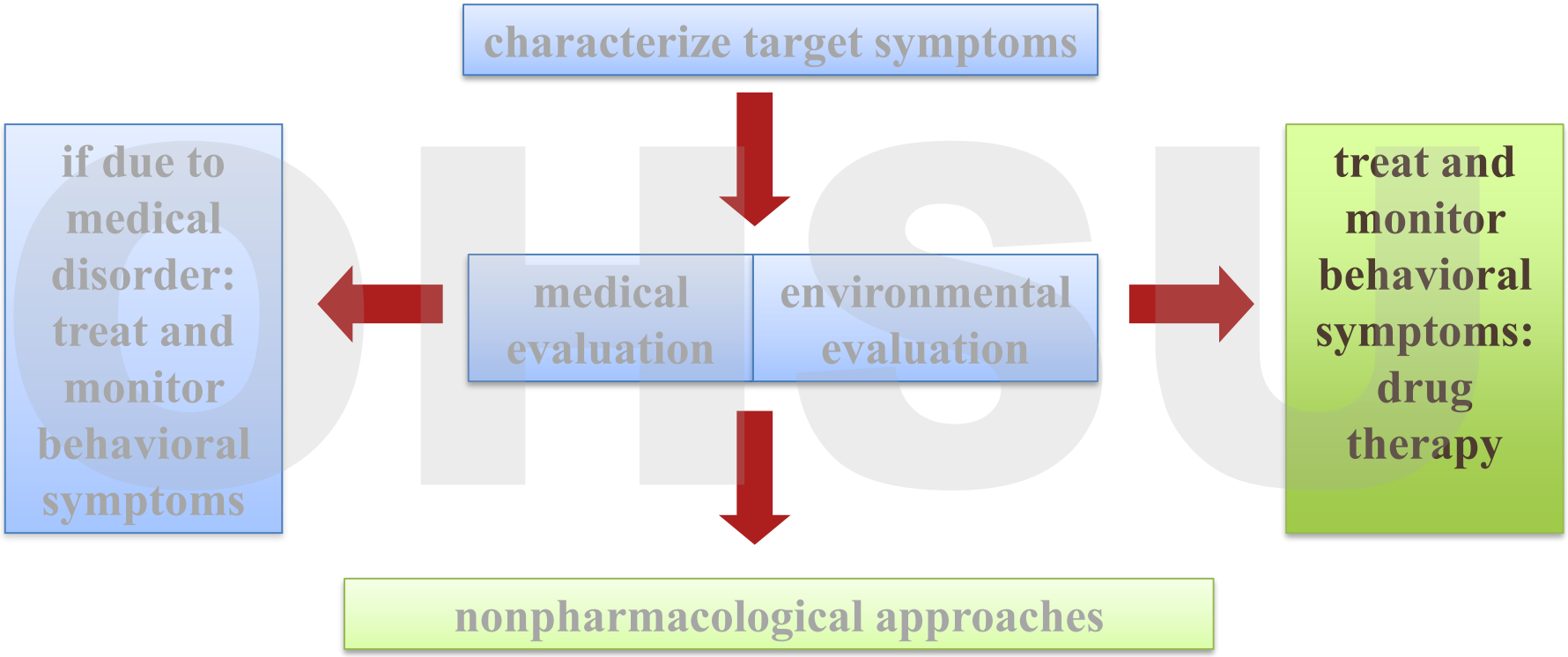


Pre-Prescribing Considerations

- 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

*Except for pimavanserin for Parkinson's disease psychosis

Pre-Prescribing Considerations

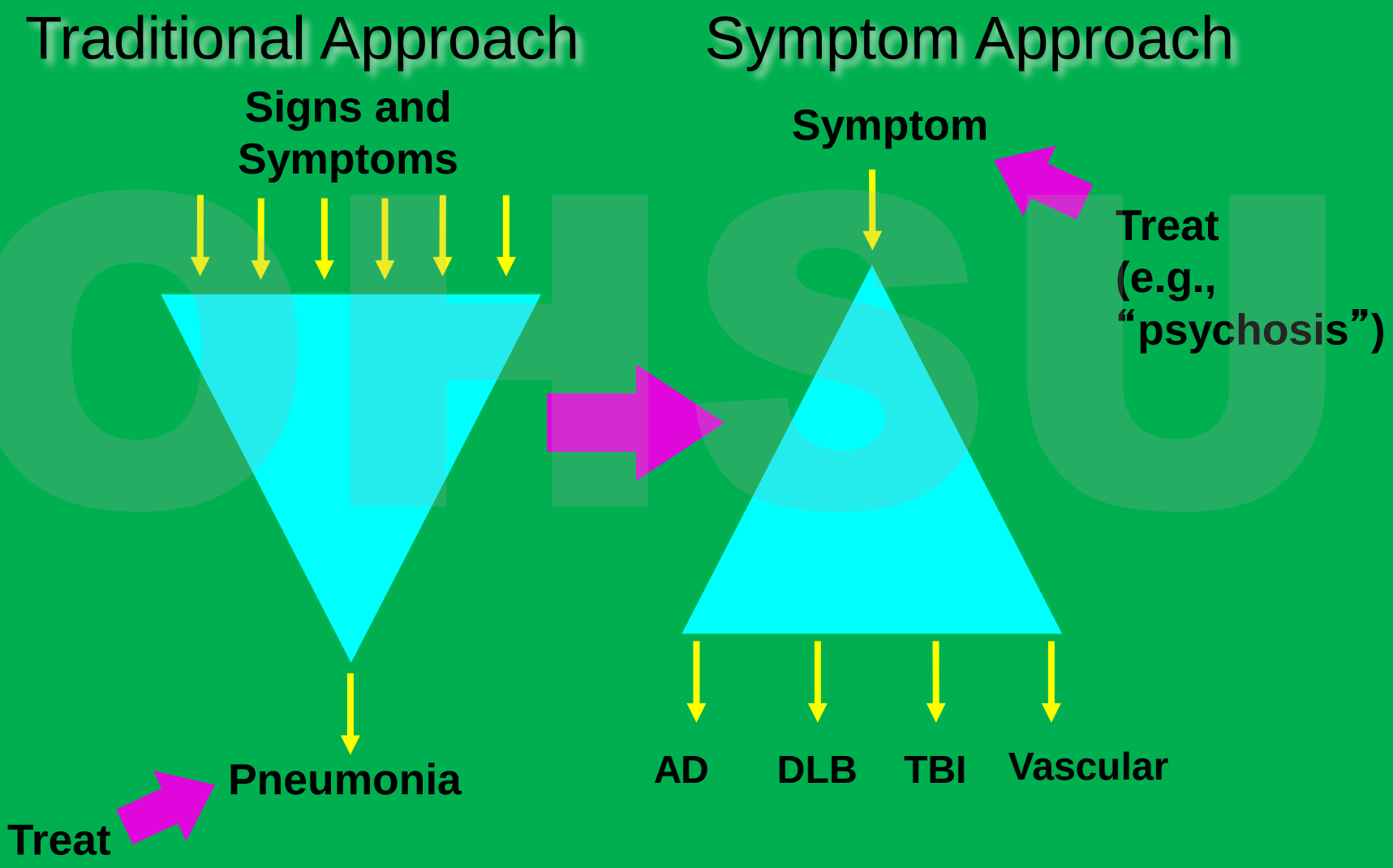
- Psychotropic medicines were developed for younger generally healthy adults without dementia
- Prescribe judiciously
  - Use the lowest effective dose for the shortest period
  - Start low and go slow (but go!)
  - Age related physiologic change -> more susceptible to side effects

Pre-Prescribing Considerations

- Ineffective medications should be stopped
  - ”Can the behavior be any worse off this medication?”
- Consider a periodic trial dose reductions of effective medications
  - “Is the medication still needed?”

SYMPTOM ORIENTED APPROACH

Symptom Oriented Approach



Symptom Oriented Approach to Treatment

- Define the target behaviors
- Look for a pattern in the patient's target symptoms analogous to what is seen in a "*drug responsive*" psychiatric syndrome

- **Psychotic** – suspicious, angry when approached, delusional
- **Depressive** – irritable, sad, vegetative, withdrawn, tearful
- **Manic** – impulsive, hypersexual, labile affect, disinhibited
- **Anxious** – worry, restless, somatic concerns, calling out

Symptom Oriented Approach to Treatment

- Match the target symptom to the drug class

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

TREATMENT

"Each capsule contains your medication,
plus a treatment for each of its side effects."

Considerations

- Multiple classes of psychotropic medication have demonstrated efficacy in treating behavioral symptoms
  - Antidepressants
  - Mood stabilizers (valproate preparations)
  - Cholinesterase inhibitors / memantine
  - Antipsychotics

Depression: Case 1

- 85-year old with early-stage Alzheimer's dementia presents to clinic with depressed mood. She describes initiation insomnia, low appetite, and anhedonia. GDS score is 10/15, supporting a diagnosis of depression. Which medication class would be reasonable to consider?
  - A. Tricyclic antidepressant
  - B. SSRI or mirtazapine
  - C. Antipsychotic
  - D. Mood stabilizer (like Depakote)

Depression: Case 1

- SSRI or mirtazapine
  - APA practice guidelines “supports undertaking one or more trials of an AD to treat clinically significant and persistent depressed mood in patients with dementia”
  - SSRIs are suggested as preferred agents but bupropion, mirtazapine, and venlafaxine are suggested options as well
    - Mirtazapine can help with sleep and appetite
    - Venlafaxine can help with comorbid pain

Antidepressants

- Start low and go slow
  - Escitalopram: 2.5mg titrated to 10mg
  - Sertraline: 25mg titrated to 200mg
  - Citalopram, 5mg titrated to 20mg
  - Mirtazapine: 7.5mg titrated to 30mg
  - Venlafaxine: 75mg titrated to 225mg
  - Duloxetine: 30mg titrated to 60mg
  - Bupropion (24h): 150mg, titrated to 450mg

Antidepressants

- Avoid tricyclic antidepressants
  - Anticholinergic, cardiac (qt prolongation, AV block, conduction delays)
- Avoid paroxetine
  - Anticholinergic
- Avoid fluoxetine
  - Long half-life and multiple drug interactions

Antidepressants – Side Effects

- Constipation
- Diarrhea
- Nausea
- Dizziness
- Dry mouth
- Falls
- Nervousness/akathisia
- Headache
- Tremor
- Decreased libido
- Gait instability
- Fatigue
- *Hyponatremia*[1]
  - Up to 12% (paroxetine)

1, Fabian TJ, Amico JA, Kroboth PD, et al. Paroxetine induced hyponatremia in older adults: a 12-week prospective study. Arch Intern Med. 2004;164:327-332.

Irritability: Case 2

- 72-year old with moderate Alzheimer's disease paces frequently throughout the day, trying to get "home." He's quick to anger, complain, and frequently refuses care; he is not physically aggressive. Which medication class would be reasonable to prescribe?
  - A. SSRI or trazodone
  - B. Antipsychotic
  - C. Cholinesterase Inhibitor
  - D. Memantine

Irritability: Case 2

- SSRI or trazodone
  - "Low harm" behavior
    - Disruptive but not dangerous
  - Generally well tolerated with low risk of serious side effects
  - Scheduled trazodone 12.5mg tid or used as needed 12.5mg tid prn

- 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"
- Guideline Update (2014): ongoing support for use of SSRIs in managing agitation

Psychosis: Case 3

- 73-year old with **dementia with Lewy bodies** who presents with a 1-year history of visual hallucinations and paranoid delusions. Which medication would you consider initiating?
  - A. Quetiapine
  - B. Risperidone
  - C. Donepezil
  - D. Memantine

Psychosis: Case 3

- Donepezil (cholinesterase inhibitor)
  - Works by increasing the levels of Ach in the synaptic cleft
  - Galantamine, rivastigmine
  - Particularly helpful for psychosis in dementia with Lewy bodies
    - First line for treatment of psychosis
    - Beneficial given the extrapyramidal side effects of antipsychotics

Psychosis: Case 3

- Quetiapine is reasonable as an alternative
  - Less binding affinity for the D2 receptor and less likely to worsen parkinsonism
    - Dose low: start 25mg and gradually work your way up to 150mg if needed
- Nuplazid (pimavanserin):
  - FDA approved for psychosis in idiopathic Parkinson's Disease
    - Can help with Lewy body dementia but expensive and hard to get approved
    - Dose: 10mg or 34mg

Cholinesterase Inhibitors

Adverse effects

- Cardiac
  - Bradycardia
  - AV Block
  - Syncope
  - QT prolongation
- GI
  - Peptic ulcer
  - Nausea
  - Vomiting
  - Diarrhea
- CNS
  - Seizures
  - Agitation
  - Hallucinations
  - Confusion

Memantine

- Memantine (Namenda)
  - FDA approved for moderate to severe Alzheimer's
  - Does it help with behaviors?
    - Literature is mixed
    - Most studies recruited patients for the purpose of testing cognition, not behavioral symptoms
  - Generally well tolerated, with cognitive and functional benefit in patients with moderate to severe dementia, worth trying if behavioral symptoms are mild
  - Side effects: dizziness, confusion, vivid dreams, hallucinations, agitation, headache

Impulsivity: Case 4

- 57-year old with behavioral variant frontotemporal dementia. The caregiver reports increased impulsive behavior, characterized by sexually inappropriate touching, labile affect, hoarding, and collecting food. Which medication would you consider?
  - A. Quetiapine
  - B. Donepezil
  - C. Valproate (Depakote)
  - D. Sertraline

Impulsivity: Case 4

- Sertraline. For impulsive or disinhibited behavior in any dementia it's reasonable to start with an SSRI.
  - Especially for FTD[1]
  - May need to optimize the dose for full response

- Can also consider valproate if already on an SSRI or an SSRI is contraindicated

1. Swartz, J. Randolph, et al. "Frontotemporal dementia: treatment response to serotonin selective reuptake inhibitors." *Journal of Clinical Psychiatry* 58.5 (1997): 212-217.

Valproate Preparations

- Consider for aggressive / impulsive behavior in the absence of psychotic symptoms or mood lability without response to other medications
  - Dose low
    - Start 125mg bid
    - Rarely exceed 1000mg per day
  - Use delayed or extended-release formulation
- Side effects: sedation, GI upset, tremor, hepatitis, thrombocytopenia
- Monitoring: LFTs, CBC

1. Rabins et al. APA Guideline Watch Practice Guideline for the Treatment of Patient's with AD and Other Dementias. 2014
2. Baillon et al. Valproate preparations for the treatment of agitated behaviour in people with dementia. *Cochrane Database Syst Rev.* 2018

Antipsychotics

Antipsychotics

- May increase mortality and stroke
  - FDA Black Box Warning (2005)
  - 1.7-fold increase in mortality compared with placebo (4.5% vs 2.6%)
  - Risk higher for 1st generation antipsychotics[1,2]
  - Olanzapine > risperidone > quetiapine[2]
  - May be dose dependent[2]
  - Risk persists[3]

1. BMJ 2012; 344.
2. J Am Geriatr Soc 58:1027–1034, 2010
3. Ballard et al. 2009).

Antipsychotics

- Benefits often still outweigh the risks in patients when treatment of psychosis and physical aggression is critical

- APA Practice Guidelines: "nonemergency antipsychotic medication should only be used for the treatment of agitation or ***psychosis*** in patients with dementia when symptoms are ***severe***, are ***dangerous***, and/or cause significant ***distress*** to the patient"

Am J Psychiatry. 2016 May 1;173(5):543-6.

Antipsychotics

- Informed consent is important!
  - Risks should be discussed
  - Patient is likely to lack decision making capacity so make sure to involve the surrogate decision maker

Antipsychotics

- If there is no clinically significant response after a 4-week trial of an adequate dose of an antipsychotic drug, the medication should be tapered and withdrawn
- If there is an adequate response of an attempt to taper and withdraw the drug should be made within 4 months of initiation

Am J Psychiatry. 2016 May 1;173(5):543-6.

Antipsychotics

- No clear difference in efficacy between drugs
- Most used
  - Olanzapine: 2.5mg (start) up to 10mg
  - Quetiapine: 25mg (start) up to 150mg
    - *Least EPS risk, dosing flexibility, helps sleep*
  - Risperidone: 0.5mg (start) up to 3mg
  - Haloperidol: 0.25mg (start) up to 3mg
    - *Most EPS risk*

Antipsychotics

- Side effects: EPS, orthostasis, akathisia, somnolence, *falls*, metabolic, cerebrovascular events, upper respiratory tract infection, cardiac events, tardive dyskinesia
- Avoid in dementia with Lewy bodies!!!
  - Start with a CI
  - Minimize dopaminergic drugs
  - Use quetiapine if an antipsychotic is needed

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.

Insomnia: Case 5

- 85-year old with moderate stage Alzheimer's disease. Her sleep wake cycle is disrupted, she's up at night and asleep during the day. Along with sleep hygiene measures, what medication might you consider?
  - A. Quetiapine
  - B. Zolpidem
  - C. Benadryl
  - D. Trazodone

Insomnia: Case 5

- Trazodone can be very helpful for sleep with low risk of side effects[1]
  - Start low (25mg one hour before desired bedtime) and titrate in 25mg increments up to 100-150mg
    - Most common side effect: orthostasis
- Melatonin
  - 300ug in the early evening to advance the sleep cycle
    - Along with bright light in the morning and daytime activity
  - 3mg-9mg 1-2 hours before desired bedtime as a hypnotic

1. Camargos EF, Louzada LL, Quintas JL, Naves JO, Louzada FM, Nobrega OT. Trazodone improves sleep parameters in Alzheimer disease patients: a randomized, double-blind, and placebo-controlled study. *Am J Geriatr Psychiatry*. 2014;22(12):1565–1574.

Benzodiazepines and Diphenhydramine

- Benzodiazepines
  - Minimal data supporting efficacy
  - Sedation, falls, cognitive impairment
  - Avoid
- Diphenhydramine
  - Common OTC sleep aid (inquire about Tylenol PM)
  - Anticholinergic
  - Sedation, falls, cognitive impairment
  - Avoid

Hypnotics

- Mirtazapine: consider if there are coexisting mood or anxiety symptoms, start 7.5mg qhs
- Magnesium 150mg – 200mg qhs

- Do no use antipsychotics solely as hypnotics
- Do not use hydroxyzine, Benadryl, or benzos!

Summary

“Pearls”

- Understand the behavior beyond just “agitation”
- 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, avoid using medicines from the same drug class)
- If lots of medications do not help, start discontinuing medications
  - Can they be any worse off medications?

“Pearls”

Reasonable Med Combos

- SRI + antipsychotic
- SRI + trazodone
- SRI + Valproate
- SSRI + bupropion
- SRI + mirtazapine (cautious)
- Antipsychotic + valproate

- +/- cholinesterase inhibitor
- +/- memantine

Med Combos to Avoid

- SSRI + SNRI
- SNRI + bupropion
- Antipsychotic + antipsychotic
- Cholinesterase inhibitor + cholinesterase inhibitor
- Valproate + gabapentin (or pregabalin)

SRI = SSRI or SNRI

“Pearls”

- Less-severe behaviors with limited consequences of harm to individual or caregiver, avoid using antipsychotics
- More severe or “high risk” behaviors such as frightening hallucinations, delusions or hitting may require addition of antipsychotic trial

The End

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Evaluation – Medical

- Discomfort / Pain
  - Musculoskeletal, constipation, urinary retention, hunger, thirst
- Review vital signs
  - Assess for infection, weight change, autonomic changes
- Medications
  - Benzodiazepines, opiates, anticholinergics, antihistamines

Evaluation – Medical

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

Evaluation - Environment

- Environment
  - Over stimulating?
    - TV, telephone, visitors, mirrors, pictures…
  - Under stimulating?
    - Dark, quiet, reduced sensory input
  - Unfamiliar
    - Transitions and changes in routine can be disruptive

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
- Weighted blanket
- 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