THE ALZHEIMER'S PROJECT CLINICAL ROUNDTABLE

Use of Medications for Management of Behavioral & Psychological Symptoms of Dementia

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- **Intro yourself**
- **No financial conflicts of interest to disclose**

Learning Objectives

- **Assess and develop** therapeutic treatment plans for behavioral and psychological signs and symptoms in patients with dementia.
- **Prescribe** appropriate and effective use of psychotropic medications in the primary care setting when needed.

DICE APPROACH TO BEHAVIORAL AND PSYCHOLOGICAL SIGNS AND SYMPTOMS OF DEMENTIA

DESCRIBE

Caregiver describes behavioral factors:

- Social & physical environment
- Patient perspective
- Degree of distress to patient and caregiver

Look for:

- Antecedents
- Patterns
- Context
- Co-occurring events

INVESTIGATE (ASSESS)

Investigate possible causes of behavior:

- Medication side effects
- Pain
- Functional limitations
- Medical conditions
- Psychiatric comorbidity
- Severity of cog impairment
- Degree of executive dysfunction
- Poor sleep
- Sensory changes
- Emotional triggers: ie,,fear, abandonment
- Lack of physical activity
- Suboptimal exposure to bright light

CREATE (TREATMENT)

Provider, caregivers, clinical team collaborate to create and implement a treatment plan

Address physical problems and medical issues first

Employ behavioral interventions

- Provide caregiver interventions
- Enhance communication
- Create meaningful activities
- Simplify tasks

Ensure that the environment is safe

Increase or decrease the amount of stimulation in the environment

If behavioral interventions not effective/partially effective, employ pharmacological management, selecting a class of psychotropic medication based on psychobehavioral "Assume/Assess/Align" model, as below

ASSUME patient does not have dementia

ASSESS psychiatric signs and symptoms

ALIGN symptoms to best fit psychiatric syndrome
eg., major depression, paranoid psychosis, mania, etc.

EVALUATE (AND RE-EVALUATE)

Evaluate whether "CREATE" interventions implemented by caregiver(s) have been safe/effective

- Make modifications as needed and continue to look for possible underlying causes
- Re-evaluate periodically
- If intervention not effective or if patient or caregiver are in danger, consider referring to neurologist or psychiatrist

Describe

Caregiver describes behavioral factors:

- Social & physical environment
- Patient perspective
- Degree of distress to patient and caregiver

Look for:

- Antecedents
- Context
- Patterns
- Co-occurring events

Investigate (Assess)

Investigate possible causes of behavior:

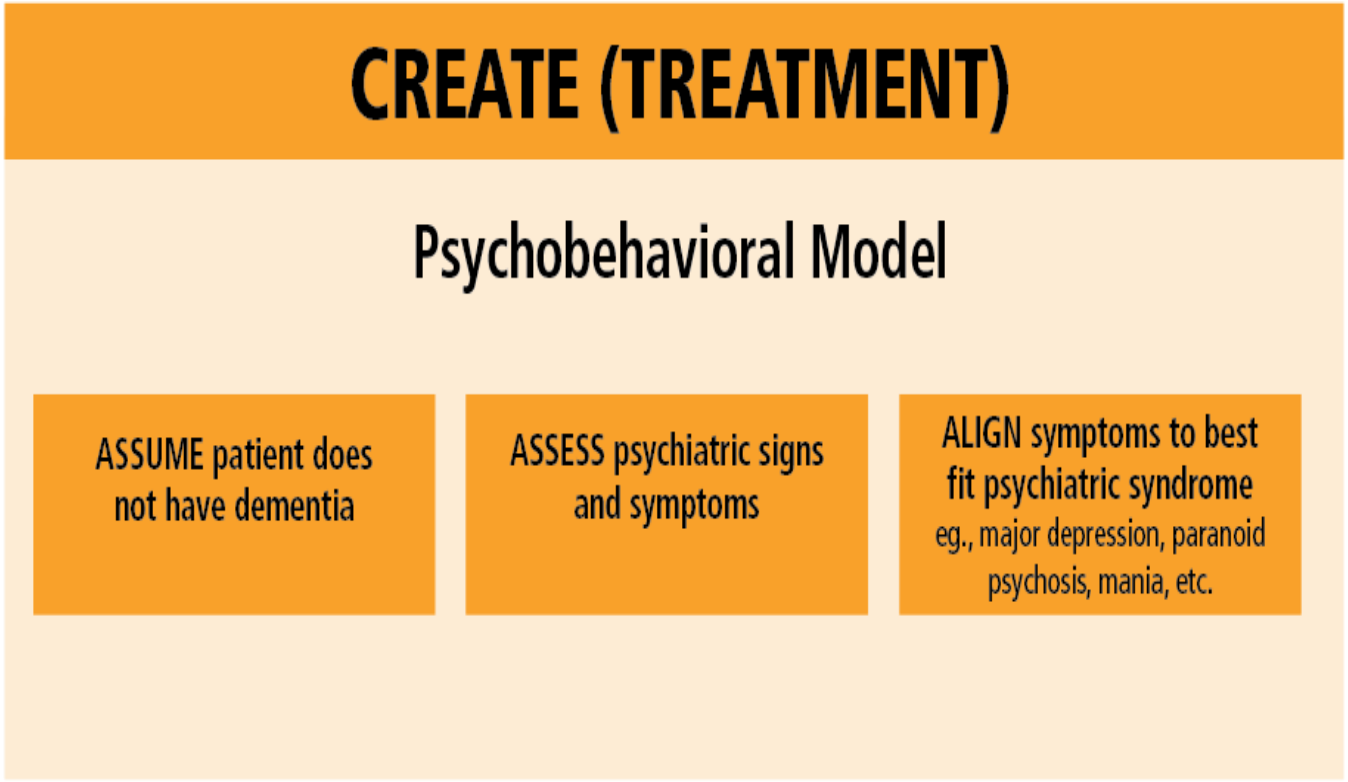
- Medication side effects
- Pain
- Physiological Needs
- Medical conditions
- Psychiatric comorbidity
- Severity of cognitive impairment
- Degree of executive dysfunction
- Poor sleep
- Sensory changes
- Emotional triggers: fear, abandonment
- Lack of physical activity
- Suboptimal exposure to bright light
- WHAT HAS CHANGED?

Create Treatment Plan

- Collaborate to create and implement a treatment plan
- Address physical problems and medical issues
- Employ behavioral interventions
  - Provide caregiver interventions, enhance communications, create meaningful activities, simplify tasks
- Ensure the environment is safe
- Increase or decrease stimulation in the environment

PSYCHOBEHAVIORAL MODEL

If Behavioral Interventions Not Effective, employ pharmacological management, selecting a class of psychotropic medication based on Psychobehavioral Model:

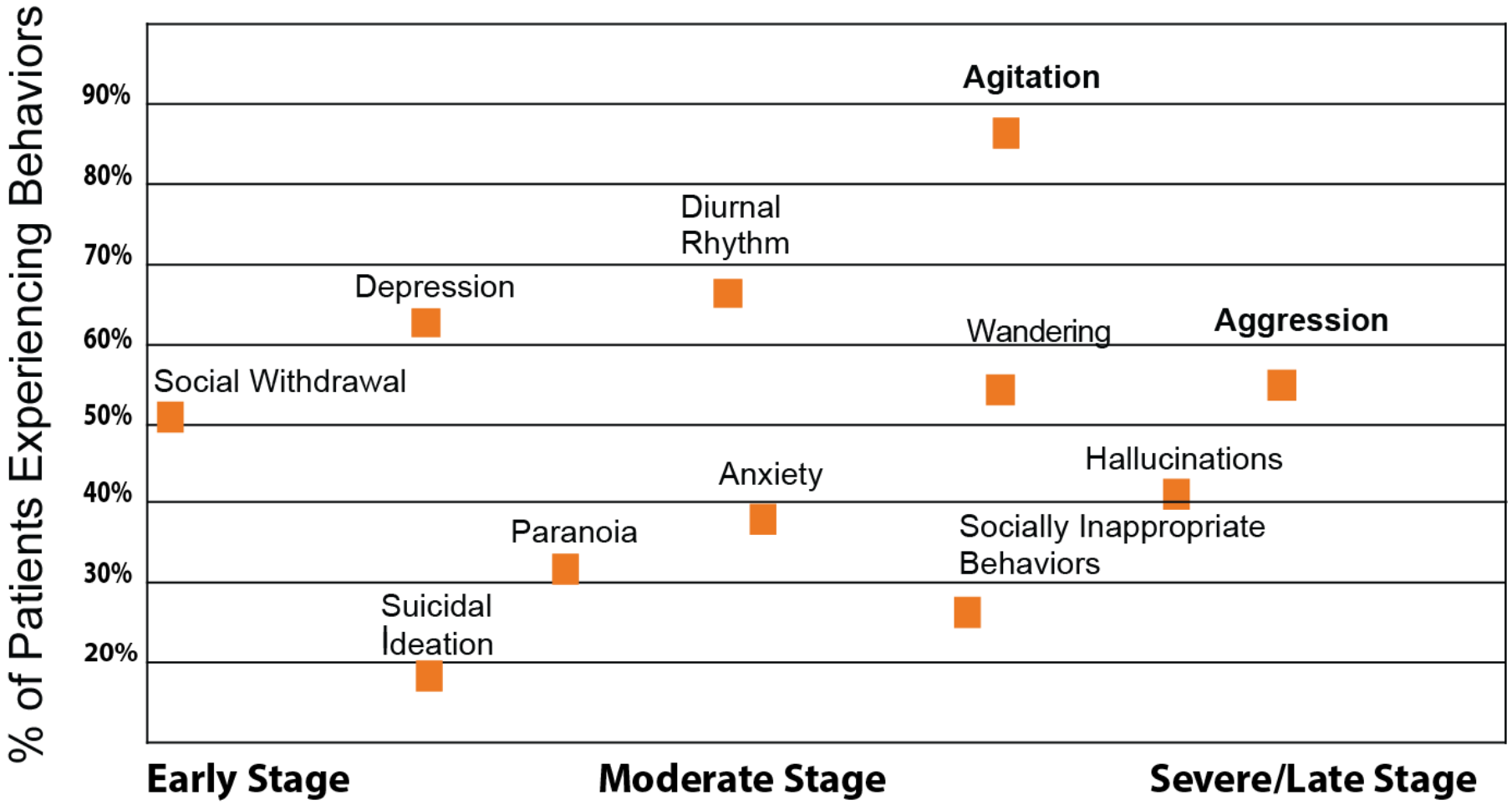


Evaluate and Re-Evaluate

Evaluate whether treatment interventions implemented by caregivers have been safe and effective

- Make modifications as needed and continue to look for possible underlying causes
- Re-evaluate periodically
- If intervention not effective or if patient or caregiver are in danger, consider referring to neurologist or psychiatrist
- Consider de-prescribing when appropriate

Peak Frequency of Behavioral Symptoms With Alzheimer's Disease Progression



Pharmacology as Second Line

- Behavioral and Environmental Interventions should be attempted prior to pharmacologic interventions
- Educate family and caregivers on effective communications, redirection, common delusions and behavioral symptoms through disease progression
- Refer to OT/PT/palliative care as appropriate to assess home environment and caregiver support

Best Practices for Prescribing

- Use medications better tolerated by older adults
- Older patients often need lower dosages
- Check timing of medication dose against other issues, i.e., diuretics
- Omission of medications
- Opioid pain medication – reduce long term use

Best Practices for Prescribing

Beers Criteria or Beers List

- List of medications more harmful than helpful for older patients
- Originally developed in 1997
- Latest versions in cooperation with American Geriatrics Society, most recent update 2023

Use of Psychotropic Medications

- Track impact of medication
- Start low dosage, Increase slowly
- Always use lowest possible dose
- Incrementally reduce dose and assess if behaviors return
- Symptoms may recede over disease progression and use of meds may not be necessary
- Review periodically; may be possible to discontinue medication
- If no response after 2nd antipsychotic, refer to psychiatry

Use of Psychotropic Medications

- For all classes of psychotropics, preference for medications that are **renally excreted**
- Benzodiazepine rarely helpful for older patients and should generally be used in a time-limited manner for situational symptoms
- May be helpful for acute agitation
- Look for meds with intermediate half-life
- Rapidly disintegrating formulation may be helpful

Antipsychotic Medications

Drug	Dose
Aripiprazole (Abilify)	4 forms including tablets (2, 5, 10, 15, 20, 30 mg), DiscMelt (10 and 15 mg), liquid and IM
Brexpiprazole (Rexulti)	Tablets (0.5 mg/day x 2 wk; 1 mg/day x 1 wk; 2 mg daily) Max dose 3 mg/day (FDA approved for agitation in dementia)
Clozapine (Clozaril)	Refer to psychiatrist
Lurasidone (Latuda)	Tablets (20, 40, 60, 80 mg)
Olanzapine (Zyprexa)	Tablets (2.5, 5, 7.5, 10, 15, 20 mg) Zydis ODT (5, 10, 15 20 mg), IM, IM ER
Paliperidone (Invega)	Tablets (1.5, 3, 6 and 9 mg) Max = 12 mg, Renal = 3 mg
Pimavanserin (Nuplazid)	Tablet 17 mg (FDA approved for Parkinson's disease psychosis)
Quetiapine (Seroquel)	Tabs (25, 50, 100, 200 mg) q 12 hours; Extended release tabs (50, 150, 200, 300, 400 mg) Consider when EPS
Risperidone (Risperdal)	4 forms including tablets and M-Tabs (0.25, 0.5, 1, 2, 3, 4 mg), liquid, Risperdal Consta (q 2 weeks)

Treatment of Emergent Agitation

If oral medications possible

- Offer risperidone: 0.25 – 1 mg dose
- OR aripiprazole: 2 – 5 mg dose
- OR olanzapine: 2.5 – 5 mg dose
- OR quetiapine: 25 – 50 mg dose
- May repeat dose 30 – 60 minutes if needed
- May need up to 3 doses of same medication before the patient responds

Treatment of Emergent Agitation

If patient refuses oral medications or is severely agitated or aggressive, choose single agent IM

- Give IM aripiprazole: 1.875 – 7.5 mg dose
- OR IM olanzapine: 2.5 – 5 mg dose
- OR IM haloperidol: 0.5 – 2 mg dose
- May repeat dose 30 – 60 minutes if needed
- May need up to 3 doses of same medication before the patient responds

Antidepressant Medications

- Vortioxetine shown to improve memory and broader cognitive function in geriatric patients with major depressive disorder (MDD), including those with comorbid early-stage dementia and Alzheimer's disease.
- Citalopram: Most likely SSRI to cause QT prolongation
- Duloxetine: Consider in case of co-morbid depression and neuropathic pain
- Venlafaxine: Short half-life can cause severe withdrawals.
- Mirtazapine: Preferred when targeting multiple symptoms including depression, anxiety, insomnia and poor appetite

These are generally considered the best choices for older adults but other factors like previous treatment history or family history may influence your choice. If you prescribed any two antidepressant medications for a particular patient without success, then a referral to a psychiatrist is recommended

Antidepressant Medications Dosage

Drug	Dose
Citalopram (Celexa)	10, 20 mg tabs (20's are scored). Starting dose is 10 mg. Max dose for seniors = 20 mg. Doses above 20 mg not recommended due to QT prolongation.
Escitalopram (Lexapro)	5, 10 and 20 mg (10 and 20s are scored). Starting dose is 5 mg. Max geriatric dose = 20.
Sertraline (Zoloft)	25, 50 100 tabs plus oral solution. Starting dose = 25 mg. Max dose = 200 mg.
Duloxetine (Cymbalta)	20, 30, 60 mg tabs. Starting dose 20 mg. Max dose = 60 mg.
Mirtazapine (Remeron) Remeron SOLTAB	7.5, 15, 30 and 45 mg tabs. Starting dose 7.5 mg Max= 45mg Orally disintegrating tab; 15, 30, 45 mg tabs
Venlafaxine	XR tabs 37.5, 75, & 150mg. Starting dose 37.5mg max 225mg
Vortioxetine	Starting dose is 5 mg, max dose of 20 mg

Mood Stabilizing Medications

Drug	Dose
Divalproex (Depakote)	Sprinkles 125; , DR 125, 250 500 mg; ER 250 and 500 mg. Oral solution: 250 mg/5 ml. Starting dose = 125 to 250 mg. Dose is determined by clinical response and blood level of **total** valproic acid (50 to 100 µg/ml). When converting to ER, increase dose by 20%.
Lithium	Tablets, capsules, oral solution; and ER. 300 mg tabs. ER comes in 300 and 450s. Solution: 8 mEq/5 ml. Recommended trough serum range is 0.4 to 0.8 mmol/L. Starting dose = 300 mg.
Gabapentin* (Neurontin)	Capsules most common 100 & 300 mg; other doses available. Starting senior dose 100 mg; Max dose = 3600 mg in a divided dose.
Pregabalin* (Lyrica)	Caps: 25 – 300 mg, Tabs, ER 82.5-330 mg, Oral Solution: 20 mg/mL.. Starting senior dose 25mg x2/day.
* Geriatric friendly and preferred to benzodiazepines	

Hypnotics/Insomnia Medications

- Melatonin
  - Use immediate release (1 to 5 mg 30-60 min prior to bedtime for sleep initiation), switch to sustained release formulation SR (1-2 mg 1-2 hours before bedtime) for sleep maintenance and awakening at night.
  - Gradual dose increases, max recommended dose 6 mg SR
  - Possible side effects: daytime drowsiness, headache, nausea, irritability, dry or itchy skin, strange dreams, night sweats
- Trazodone: Dose range: 25 - 200 mg
- Mirtazapine: lower doses (7.5-15 mg) are more sedating, higher doses (> 30 mg) have more activating properties through central α2-adrenergic antagonis

Hypnotics/Insomnia Medications

- Dual orexin receptor antagonists safer than benzodiazepines, prescribe use 30 min prior to bedtime
  - Suvorexant: 5 mg to 20 mg nightly
  - Lemborexant: 5 to 10 mg nightly
  - Daridorexant: 25 – 50 mg nightly
- Discuss risk and benefits

Hypnotics Not Recommended: Z Drugs

- Zolpidem, zaleplon, eszopiclone, and zopiclone, are NOT recommended due to an unfavorable risk-benefit profile.
- They do provide modest short-term improvements in sleep parameters such as total sleep time and sleep onset latency in older adults, including those with dementia and comorbid depression or cognitive impairment, but their use is associated with significant safety concerns including higher risk of daytime sedation, worsened agitation, cognitive impairment, falls and fractures.
- Overall, they should generally be avoided or used only with extreme caution and close monitoring.

Hypnotics Not Recommended:Benzodiazepines

- NOT recommended due to an unfavorable risk-benefit profile. While short-term sleep outcomes may improve in some older adults, adverse effects including confusion, disorientation, and increased risk of injurious fall outweigh any potential benefit, especially in those with cognitive impairment.
- Benzodiazepines can be considered for short term emergencies to complete imaging (CT/MRI) or small dental procedures.
- Relatively preferred benzodiazepines:
  - Lorazepam (Ativan®)
  - Oxazepam (Serax®)
  - Temazepam (Restoril®)
  - Occasionally may use clonazepam (Klonopin®)

Ongoing Research: Prazosin

- Prazosin is an alpha-1 receptor antagonist
  - A small placebo-controlled trial was found that it is helpful in treating agitation in nursing home residents with AD, but not generally recommended
  - The only alpha-1 antagonist that crosses blood/brain barrier
  - Non-sedating
  - Does not cause parkinsonism
  - Shown to have long-lasting benefits in PTSD
  - **High risk of orthostatic hypotension and falls**
- Excessive noradrenergic reactivity produces anxiety and agitation and may contribute to agitation in individuals living with AD

Ongoing Research: Dextromethorphan-Quinidine

Dextromethorphan hydrobromide and quinidine sulfate (Nuedexta®) is approved for pseudobulbar affect (PBA) in the US and European Union

- Dextromethorphan
  - Most well-known as a cough suppressant
  - a low low-affinity, uncompetitive NMDA receptor antagonist
  - σ_1 (sigma$_1$) receptor agonist
  - Serotonin and norepinephrine reuptake inhibitor
  - Neuronal nicotinic α_3 β_4 receptor antagonist
- Quinidine
  - is a Class 1 antiarrhythmic
  - When *combined* with *dextromethorphan*, *quinidine* works by increasing the amount of *dextromethorphan* in the body

Ongoing Research: Dextromethorphan-Quinidine

- Dosing in PBA
  - The combination of dextromethorphan (20 mg) - quinidine (10 mg) comes as a capsule to take by mouth.
  - Taken with or without food
  - Starting dose: 1x day for 7 days
  - After 7 days, it is taken every 12 hours
  - More than 2 doses should not be taken in a 24-hour period
  - 12 hours between each dose
  - Should be taken at around the same time(s) every day
  - **Important drug-drug interactions**: desipramine (levels increase 8-fold), paroxetine (2-fold increase), MAOIs and memantine

Ongoing Research: Cannabinoids

Cannabinoids are not recommended

- Behaviors improved in some small-scale studies: agitation, aggression, impulsivity, nocturnal restlessness, wandering, and poor sleep
- Sedation was most commonly reported adverse effect, followed by delirium and urinary tract infection
- Discuss risks and benefits; increased use by older adults
- Risk of psychosis is increased with THC-containing cannabinoids in older adults, particularly in those with dementia or cognitive impairment especially at higher doses or with prolonged use

Summary:

- Start with DICE model to assess behavior
- Initiate behavioral and other non-pharmacological interventions
- If inadequate response, remember principles of senior prescribing:
  - Start low, go slow
  - Start with a single agent, avoid poly-pharmacy
  - Use medications better tolerated by older adults
  - Older patients often need lower dosages
  - Re-evaluate as appropriate

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Funding for this educational series provided by

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This project is supported by the Health Resources and Services Administration (HRSA) of the U.S. Department of Health and Human Services (HHS), as part of grant number U1QHP53055, Geriatric Workforce Enhancement Project award totaling $5 million. The contents are those of the author(s) and do not necessarily represent the official views of, nor an endorsement, by HRSA, HHS or the U.S. Government.