Beyond Memory Loss: Mastering the Management of Behavioral Symptoms in Dementia

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Learning Objectives

1. Identify clinical characteristics of the behavioral symptoms of dementia (BSD) including agitation, psychosis, and sleep disturbances
2. Discuss medications currently used in the management of BSD along with emerging pharmacologic therapy options
3. Determine the most appropriate pharmacologic treatment option for a patient with behavioral symptoms of dementia based on patient-specific factors

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Disclosures

- Dr. Waters is a paid speaker for Johnson & Johnson. All financial interests with ineligible companies have been mitigated

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Disclosures

- This presentation will include discussion of off-label use of the following medications:
  - Antipsychotics including pimavanserin
  - Dual orexin receptor antagonists
  - Dextromethorphan-quinidine, dextromethorphan-bupropion, deuterated dextromethorphan-quinidine
  - SL dexmedetomidine
- The content and views presented in this educational program are those of the faculty and do not necessarily represent those of University of Connecticut School of Pharmacy. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications, and warnings.

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Behavioral Symptoms of Dementia

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Background: Types of Dementia

- **Alzheimer's disease (AD):** 60-80% of dementia cases
- **Vascular dementia:** 5-10% of dementia cases
- Other types of dementia:
  - Lewy body dementia
  - Frontotemporal dementia
  - Parkinson's disease dementia
  - Mixed dementia

Goodman RA, et al. *Alzheimers Dement.* 2016
2024 Alzheimer's disease facts and figures. *Alzheimers Dement.* 2024

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Core Dementia Symptoms

- **Decline in cognitive function**
  - Memory
  - Reasoning
  - Concentration
  - Communication
  - Executive functioning
- Motor disturbances
- Personality changes
- Behavioral symptoms

Teixeira AL, et al. *Arq Neuropsiquiatr.* 2023
American Psychiatric Association. *DSM-5-TR.* 2013

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Behavioral Symptoms of Dementia (BSD)

- Often assessed using Neuropsychiatric Inventory tool

Domain	Behavioral Symptoms
Affective	Apathy Anxiety Depression/dysphoria
Agitation	Motor behavior Aggression
Psychosis	Delusions Hallucinations
Sleep disorders	Insomnia Hypersomnia Restless leg syndrome
Disinhibition	Impulsivity Socially inappropriate behaviors (including sexual)

Teixeira AL, et al. *Arq Neuropsiquiatr.* 2023 de Medeiros K, et al. *Int Psychogeriatr.* 2010

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Behavioral Symptoms of Dementia (BSD)

- Variable prevalence across dementia subtypes
  - Psychosis: Lewy body > AD
  - Inappropriate social behaviors: Frontotemporal > other subtypes
- BSD often more severe when cognitive symptoms worsen
- Apathy, delusions, and agitation likely most common forms of BSD

Teixeira AL, et al. *Arq Neuropsiquiatr.* 2023

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Adverse Outcomes of BSD

- Worsening cognitive and functional decline
- Caregiver burden
- Cost
- Utilization of medical service
- Institutionalization
- Death

Teixeira AL, et al. *Arq Neuropsiquiatr.* 2023 Feast A, et al. *Int Psychogeriatr.* 2016 Sabates J, et al. *Neuropsychol Rev.* 2024

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Agitation in Dementia

- May impact >50% of patients with dementia
  - Higher rate in nursing homes
- Features of agitation may include:
  - Pacing
  - Restlessness
  - Repetitive motor and vocal behaviors
  - Aggression (physical or verbal)
    - Hitting, scratching, biting, throwing objects
- May follow circadian rhythm ("sundowning")

Teixeira AL, et al. *Arq Neuropsiquiatr.* 2023 de Medeiros K, et al. *Int Psychogeriatr.* 2010 Selbaek G, et al. *Int Psychogeriatr.* 2014

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Psychosis in Dementia

- Includes delusions and hallucinations
  - Reported in >50% of patients with AD (delusions > hallucinations)
- Can last for many months
- May be distressing

Delusions	Hallucinations
• Persecutory • Religious • Jealousy **Misidentifications:** • Capgras (hypofamiliarity) • Phantom boarder syndrome • Reduplication	• **Visual** (simple or complex) • Auditory • Tactile • Olfactory

Teixeira AL, et al. *Arq Neuropsiquiatr.* 2023 Pessoa RMd, et al. *Dement Neuropsychol.* 2023 Ropacki SA, et al. *Am J Psychiatry.* 2005

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Sleep Disorders in Dementia

- Sleep disorders in older patients are a risk factor and predictor for cognitive impairment and dementia
  - Up to 70% of people with AD have a sleep disorder
    - Higher risk in Lewy body dementia
  - Sleep deficits worsen cognitive symptoms
  - Sleep-wake cycle important in production and clearance of proteins relevant to AD
- **Most common:**
  - Insomnia
  - Sleep-disordered breathing
  - Restless leg syndrome
  - Rapid eye movement (REM) sleep behavior disorder

Teixeira AL, et al. *Arq Neuropsiquiatr.* 2023 Casagrande M, et al. *In J Environ Res Public Health.* 2022 Zhao QF, et al. *J Affect Disord.* 2016 Koren T, et al. *Ageing Res Rev.* 2023 Gao F, et al. *Neurosci Lett.* 2021

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Affective Symptoms of Dementia

- Apathy = **most common behavioral disorder**
  - Up to 90% in AD
  - Loss of motivation for goal-directed behaviors and cognitive activities
  - Blunted affect
  - Associated with cognitive and functional decline, caregiver burden, institutionalization, mortality
- Depression
- Anxiety

Teixeira AL, et al. *Arq Neuropsiquiatr.* 2023

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Audience Question 1

Which of the following is a symptom of agitation in dementia?

A. Hallucinations

B. Restless leg syndrome

C. Throwing objects

D. Religious preoccupation

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Audience Question 1

Which of the following is a symptom of agitation in dementia?

A. Hallucinations

B. Restless leg syndrome

C. Throwing objects

D. Religious preoccupation

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Current Management of BSD

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Goals of Treatment

4 — **Define presence and severity of each behavior**

5 — **Identify any causative or aggravating factors**
- Sensory deprivation or overstimulation
- Physical discomfort
- Medical comorbidity

6 — **Identify non-pharmacologic and pharmacologic interventions**

Kales HC, et al. *Int Psychogeriatr.* 2019 Teixeira AL, et al. *Arq Neuropsiquiatr.* 2023

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Non-Pharmacologic Management of BSD

First-line

Mostly focused on caregiver techniques:

- Identify **ABC**s of behavioral changes:
  A: Antecedent or triggering event that precedes behavior
  B: Problem behavior
  C: Consequences of the behavior

Non-pharmacologic therapies:

- Encourage activities that patient enjoys
- Redirect and refocus (intervene early)
- Increase social activities
- Eliminate sources of conflict and frustration

Reus VI, et al. *Am J Psychiatry.* 2016 NICE Guidelines: Dementia: assessment, management, and support for people living with dementia and their carers. 2018

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Consider Concurrent Medications

- If possible, goal should be to minimize:
  - Anticholinergic load
  - Corticosteroids
  - Benzodiazepines
  - Opioids
  - Z drugs

Bishara D, et al. *Int J Geriatr Psychiatry.* 2014

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Pharmacologic Management of BSD

- **Only after non-pharmacologic treatment has been ineffective**
- Should generally still be combined with non-pharmacologic treatment
- **Overarching guideline recommendations:**
  - Any medication used should be part of a comprehensive treatment plan
  - Weigh risks vs. benefit
  - Taper off if no improvement after 4-week trial at adequate dose
  - Attempt taper within 4 months if have positive response

Reus VI, et al. *Am J Psychiatry.* 2016 NICE Guidelines: Dementia: assessment, management, and support for people living with dementia and their carers. 2018

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Management of Agitation

1. Intervene early and recognize the patient's behavior
2. Stay calm during the interaction and avoid arguing or reasoning with the patient
3. Approach the patient from the front with slow movements and sit or stand with the patient at eye level
4. Redirect and refocus by distracting the patient, asking about the problem, and gradually turning their attention to something pleasant. Possibly move the patient to a quieter room or activity.

Reus VI, et al. *Am J Psychiatry.* 2016 NICE Guidelines: Dementia: assessment, management, and support for people living with dementia and their carers. 2018

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Pharmacologic Management of Agitation

Weak data:

- Antidepressants (primarily SSRIs)
  - Citalopram
  - Trazodone
- Carbamazepine

Antipsychotics

- Only in cases of agitation that is **severe**, **dangerous**, and/or causes **significant distress** to patient
- NOT appropriate for insomnia, pacing, apathy

Avoid=

- Valproate
- Lithium
- Oxcarbazepine
- Tricyclic antidepressants
- Mirtazapine?
  - No improvement vs. placebo in recent study of AD patients

Reus VI, et al. *Am J Psychiatry.* 2016 NICE Guidelines: Dementia: assessment, management, and support for people living with dementia and their carers. 2018
Banerjee S, et al. *Health Technol Assess.* 2023

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Pharmacologic Management of Psychosis

- Antipsychotics
  - Second-generation antipsychotics (SGAs) preferred
    - First-generation likely as effective but higher mortality risk
    - Higher-potency agents more likely to worsen movement-related symptoms
- **Commonly used:** Risperidone, olanzapine, quetiapine, aripiprazole, brexpiprazole
  - Data is mixed regarding most effective agent and whether antipsychotics adequately treat psychotic symptoms in dementia
    - Possible increased risk of mortality

Teixeira AL, et al. *Arq Neuropsiquiatr.* 2023 Yanusa J, et al. *Adv Ther.* 2022

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General Guidelines: Antipsychotics & BPSD

- Start at **low dose** and titrate to **minimum effective dose** as tolerated
- Taper and discontinue after **4 weeks** if no improvement
- SGAs used more often:
  - Risperidone approved for BPSD in some countries (not U.S.)
  - **Brexpiprazole** FDA-approved for the treatment of agitation associated with dementia due to Alzheimer's disease in 2023
- **Avoid:**
  - Haloperidol
  - Long-acting injectable antipsychotics

Reus VI, et al. *Am J Psychiatry*. 2016 Brexpiprazole [package insert]. Rockville, MD: Otsuka America Pharmaceutical, Inc.; 2023

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Reminder: Antipsychotic Boxed Warning

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS and SUICIDAL THOUGHTS AND BEHAVIORS

See full prescribing information for complete boxed warning.

- **Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at increased risk of death. REXULTI is not approved for the treatment of patients with dementia-related psychosis without agitation associated with dementia due to Alzheimer's disease. (5.1)**

Brexpiprazole [package insert]. Rockville, MD: Otsuka America Pharmaceutical, Inc.; 2023

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Antipsychotics in Non-AD Dementia

- Lewy body dementia and Parkinson's disease dementia:
  - Antipsychotics may worsen motor features
  - More sensitive to adverse effects

NICE Guidelines: Dementia: assessment, management, and support for people living with dementia and their carers. 2018

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Brexpiprazole & Agitation in AD

- FDA-approved in 2023 as **scheduled** treatment for agitation associated with AD

Evidence leading to approval:

- 2 randomized, 12-week, parallel-arm, double-blind, placebo-controlled, multi-site studies
  - Study 1: Fixed-dose brexpiprazole 1mg or 2 mg/day
  - Study 2: Flexible-dose brexpiprazole 0.5-2mg/day
- Included adults 55-90 years of age with diagnosis of probable AD with baseline symptoms of agitation or aggression

Grossberg GT, et al. *Am J Geriatr Psychiatry*. 2020

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Brexpiprazole & Agitation in AD

- Primary outcome: Change in Cohen-Mansfield Agitation Inventory (CMAI) from baseline to week 12

Treatment Group	Baseline Mean CMAI Score	Change from Baseline at Week 12, Adjusted Mean (SE)	P-value	Cohen's d Effect Size
Study 1: Fixed-dose				
Brexpiprazole 2 mg (n=138)	71.0	-21.6 (1.3)	0.040	-0.25
Brexpiprazole 1 mg (n=134)	70.5	-17.6 (1.3)	0.90	0.02
Placebo (n=131)	72.2	-17.8 (1.3)		
Study 2: Flexible-dose				
Brexpiprazole 0.5-2mg*	71.5	-18.9 (1.2)	0.15	-0.18
Placebo	68.6	-16.5 (1.1)		

*Post-hoc analysis found statistically significant improvement among subjects titrated to 2 mg by week 4

Grossberg GT, et al. *Am J Geriatr Psychiatry*. 2020 Meunier J, et al. *Front Neurol*. 2024

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Brexpiprazole & Agitation in AD

FIGURE 3. Primary endpoint in Study 1: effects of brexpiprazole on symptoms of agitation (CMAI Total).

Notes: MMRM analysis. Mean (SD) CMAI Total score at baseline: placebo, 72.2 (17.9); brexpiprazole 1 mg, 70.5 (16.0); brexpiprazole 2 mg, 71.0 (16.6). CMAI: Cohen-Mansfield Agitation Inventory; MMRM: mixed model for repeated measures; SD: standard deviation; SE: standard error. *$t_{(318)} = -2.06$, p = 0.040 versus placebo.

FIGURE 5. Primary endpoint in Study 2: effects of brexpiprazole on symptoms of agitation (CMAI Total) in a) total efficacy sample and b) subgroup titrated to 2 mg (or equivalent placebo) at Week 4 (post hoc analysis).

Grossberg GT, et al. *Am J Geriatr Psychiatry*. 2020

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Audience Question 2

A 64-year-old patient has a PMH of AD, hypertension, urinary incontinence, and insomnia. Recently, they have been increasingly agitated throughout both the day and night. Symptoms primarily include pacing and verbally repeating the same phrases many times. Non-pharmacologic intervention is mildly effective, but the patient's caregiver is requesting pharmacologic intervention as well.

Current medications:

- Amlodipine 10 mg po daily
- Oxybutynin 10 mg po daily
- Diphenhydramine 25 mg po nightly prn insomnia
- Cetirizine 10 mg po daily
- Melatonin 6 mg po nightly

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Audience Question 2

Which of the following is the best first step in managing the patient's agitation?

A. Discontinue melatonin

B. Reduce anticholinergic load

C. Initiate mirtazapine

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Audience Question 2

Which of the following is the best first step in managing the patient's agitation?

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Audience Question 3

The patient and caregiver agree to discontinuation of the cetirizine and diphenhydramine. They feel strongly that the oxybutynin improves their quality of life by allowing them to not become incontinent of urine overnight. Unfortunately, several weeks later the agitation symptoms persist. Which of the following is the best recommendations at this time?

A. Initiate citalopram

B. Initiate haloperidol

C. Initiate risperidone

D. Initiate valproate

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Audience Question 3

The patient and caregiver agree to discontinuation of the cetirizine and diphenhydramine. They feel strongly that the oxybutynin improves their quality of life by allowing them to not become incontinent of urine overnight. Unfortunately, several weeks later the agitation symptoms persist. Which of the following is the best recommendations at this time?

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Pharmacologic Management of Sleep Disorders

- Limited data
- Guidelines recommend against use of melatonin although commonly used
  - No positive evidence for melatonin receptor agonists (ramelteon)
- Significant adverse effects associated with benzodiazepines, Z drugs
- **Preferred**:
  - Trazodone
  - Orexin receptor antagonists

NICE Guidelines: Dementia: assessment, management, and support for people living with dementia and their carers. 2018 Teixeira AL, et al. *Arq Neuropsiquiatr.* 2023 Javed B, et al. *Expert Rev Neurother.* 2023

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Orexin Receptor Antagonists in Dementia

Orexin (hypocretin): Neuropeptides that modulates sleep-wake cycle

- Higher levels = increased wakefulness

Orexin system may be dysregulated in dementia

- Positive correlation between biomarkers of AD and orexin levels

Gao F, et al. *Neurosci Lett.* 2021 Suvorexant [package insert]. Whitehouse Station, NJ: Merck & Co., Inc.; 2014

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Orexin Receptor Antagonists in Dementia

- Currently available medications are **dual** orexin receptor antagonists (DORAs) → antagonize orexin-1 and orexin-2 receptors
  - Suvorexant
    - FDA-approved for sleep disorders in AD in 2020
  - Lemborexant
  - Daridorexant
- Seltorexant = selective orexin-2 receptor antagonist
  - In phase 2 studies for probable AD with clinically significant agitation/aggression

Gao F, et al. *Neurosci Lett.* 2021 Suvorexant [package insert]. Whitehouse Station, NJ: Merck & Co., Inc.; 2014

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DORAs in Dementia

Suvorexant	Lemborexant
Phase III randomized, double-blind, placebo-controlled trial (N=285) • Included pts with mild-to-moderate probable AD • Sleep assessed by overnight polysomnography in sleep laboratory • Improvement in total sleep time of 28 minutes compared to placebo ($p<0.01$) after 4 weeks Case series (n=4) reported improvement in "nocturnal delirium" in AD for pts who had failed other pharmacologic options	Phase II randomized, double-blind, placebo-controlled trial (N=62) • Included pts with diagnosis of AD and irregular sleep-wake rhythm disorder • 3 out of the 4 doses studied statistically significantly reduced number of limb movements (restlessness) after 4 weeks • Decrease in sleep during the day for 2 of 4 doses studied

Roland JP, et al. *Drugs Aging.* 2021 Herring WJ, et al. *Alzheimers Dement.* 2020 Hanazawa T, et al. *Clin Psychopharmacol Neurosci.* 2019 Moline M, et al. *J Prev Alzheimers Dis.* 2021

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Pharmacologic Management of Affective Symptoms

SSRIs

Trazodone

Teixeira AL, et al. *Arq Neuropsiquiatr.* 2023

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Emerging Therapies

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Emerging Therapies

Pimavanserin

Dextromethorphan combination medications

Dexmedetomidine

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Pimavanserin (Nuplazid) & BSD

- FDA-approved in 2016 for Parkinson's disease psychosis (PDP)
- Considered a second-generation antipsychotic, however very different mechanism:
  - Inverse agonist and antagonist of 5-HT_{2A} and 5-HT_{2C} receptors
  - Negligible affinity for dopamine receptors
- In trial of PDP, results showed that patients with cognitive impairment had more robust response to treatment
  - Now being studied for treatment of dementia-related psychosis

Pimavanserin [package insert]. San Diego, CA: Acadia Pharmaceuticals Inc.; 2023 Espay AJ, et al. *Mov Disord.* 2018

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Pimavanserin and Dementia-Related Psychosis

- Phase II trial showed efficacy in psychosis in possible or probable AD after 6 weeks (but not after 12 weeks)
- Phase III trial (HARMONY trial) of pimavanserin 34 mg daily:
  - 12-week open-label period followed by double-blind placebo-controlled period of up to 26 weeks for patients who met criteria for treatment response
  - Included adults 50-90 years of age who met criteria for Parkinson's disease dementia, Lewy body dementia, AD, frontotemporal dementia, or vascular dementia
    - Psychotic symptoms for $\geq$ 2 months

Ballard C, et al. *Lancet Neurol.* 2018 Tariot PN, et al. *N Engl J Med.* 2021

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HARMONY Trial, Continued

- Primary endpoint: Time from randomization to relapse of psychosis
- N=392 in open-label phase
- N = 217 in double-blind phase
- Primary dementia subtypes: AD > PDP> vascular > Lewy body > frontotemporal
- **Relapse rate at time of interim analysis (statistically significant):**
  - 13% in pimavanserin group
  - 28% in placebo group
- **Fewer patients discontinued pimavanserin** (22%) compared to placebo (38%)

Ballard C, et al. *Lancet Neurol.* 2018 Tariot PN, et al. *N Engl J Med.* 2021

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Audience Question 4

A 71-year-old patient with vascular dementia recently started voicing the belief that unknown people were living in his attic. He states that he can hear the intruders talking during the night but they are able to hide whenever someone goes up to check. The patient is extremely distressed about this and is trying to obtain a firearm to protect his family from these intruders.

Which of the following pharmacologic recommendations may be appropriate? Select all that apply.

A. Brexpiprazole
B. Trazodone
C. Pimavanserin
D. Citalopram
E. Haloperidol

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Audience Question 4

A 71-year-old patient with vascular dementia recently started voicing the belief that unknown people were living in his attic. He states that he can hear the intruders talking during the night but they are able to hide whenever someone goes up to check. The patient is extremely distressed about this and is trying to obtain a firearm to protect his family from these intruders.

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A. Brexpiprazole
B. Trazodone
C. Pimavanserin
D. Citalopram
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Audience Question 5

The patient has significant improvement in symptoms following the initiation of brexpiprazole. However, they are still very restless at night and wake up frequently. They report being "exhausted" each day. Which of the following would be the best pharmacologic option?

A. Quetiapine
B. Melatonin
C. Eszopiclone
D. Suvorexant

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Audience Question 5

The patient has significant improvement in symptoms following the initiation of brexpiprazole. However, they are still very restless at night and wake up frequently. They report being "exhausted" each day. Which of the following would be the best pharmacologic option?

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B. Melatonin

C. Eszopiclone

D. Suvorexant

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Dextromethorphan (DTX) & BSD

- DTX: Multiple mechanisms:
  - Uncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist
  - Sigma-1 receptor agonist
  - Serotonin and norepinephrine reuptake inhibitor
  - Nicotinic receptor antagonist
- Mechanism in BSD unclear
- May be formulated with CYP2D6 inhibitors (quinidine, bupropion) to inhibit metabolism and extend bioavailability

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Dextromethorphan (DTX) Combinations

	DTX-Quinidine	Deuterated DTX-quinidine	DTX-Bupropion
Brand name	Nuedexta	N/A (AVP-786)	Auvelity
FDA-approved indications	Psuedobulbar affect	N/A	Major depressive disorder
Studies in dementia	**Phase 2 study: Probable AD with agitation** • N=220 • Significant reduction in agitation/aggression scores compared to placebo after 10 weeks	**Two phase 3 studies: Moderate-to-severe agitation and probable AD** • Contradictory results • Full datasets not published **TRIAD-1:** Statistically significant decrease in agitation (N=410) with one of the two doses assessed after 12 weeks **TRIAD-2:** Did not replicate findings of TRIAD-1 in similar patient population (N=522)	Currently in trials for agitation related to AD Early data suggests significant reduction in agitation symptoms in AD
Common ADEs	Falls Diarrhea UTI	Sinus bradycardia Nausea, vomiting UTI Falls Agitation	Diarrhea Xerostomia Headache Sexual dysfunction Dizziness

Khoury R. *Neural Regen Res.* 2022   Ward K, et al. *Expert Opin Investig Drugs.* 2022   Cummings JL, et al. *JAMA* 2015

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Dexmedetomidine & BSD

- FDA-approved **sublingual** dexmedetomidine in 2022 for agitation associated with schizophrenia or bipolar disorder
- Studies investigating use in BSD:
  - **TRANQUILITY II:** Phase 3
    - Treatment of acute psychomotor agitation (kicking, biting, flailing) in dementia
    - One of the two doses studied is reported to have shown significant reduction in Positive and Negative Syndrome Scale-Excited Component (PEC) score 1 hour and 2 hours after administration
  - **TRANQUILITY III:** Phase 3
    - Probable AD and resided in care facility → terminated early
  - **Planned:** Phase 2 study assessing dexmedetomidine transdermal patch

Murphy KS, et al. *J Am Geriatr Soc.* 2024.

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Summary of Emerging Therapies:

Psychosis in dementia:

- <u>May be helpful:</u>
  - Pimavanserin → phase 3 trials showed lower relapse and discontinuation rates in psychosis associated with multiple types of dementia vs. placebo

Agitation in dementia:

- <u>May be helpful **in AD**:</u>
  - DTX-quinidine → phase 2 study showed reduction in agitation/aggression vs. placebo
- <u>Not enough data:</u>
  - Deuterated DTX-quinidine
  - DTX-bupropion
  - Dexmedetomidine (SL)

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Summary

	Agitation	Psychosis	Sleep
Current therapy	• Antidepressants • Carbamazepine • Antipsychotics if severe, dangerous, or causing significant distress	• Second-generation antipsychotics	• Trazodone • Dual orexin receptor antagonists
Emerging therapy	• DTX-quinidine • *Deuterated DTX-quinidine* • *DTX-bupropion* • *Dexmedetomidine (SL)*	• Pimavanserin	• Orexin receptor antagonist (may be more for agitation)

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Summary

1. Agitation, psychosis, and sleep disturbances are distinct behavioral symptoms of dementia that require separate assessment and treatment
2. Antipsychotics should be reserved for cases of psychosis or for agitation that is severe, dangerous, or causes significant distress
3. New treatment options may become available to help target BSD in the future

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Beyond Memory Loss: Mastering the Management of Behavioral Symptoms in Dementia

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