Pharmacological Treatment of Behavioral and Psychological Symptoms of Dementia

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Psychiatry for Non-Psychiatrists

Disclosure

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I do not have any financial relationships with ineligible companies to disclose

I will be discussing off-label use of a commercial product

Learning Objectives

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- Describe the various types of behavioral and psychological symptoms of dementia
- Discuss psychopharmacological treatments for the behavioral and psychological symptoms of dementia
- Explore some of the risks and adverse effects related to psychopharmacological treatments used to treat behavioral and psychological symptoms of dementia

Dementia (Major Neurocognitive Disorder)

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- Unusual to see prior to 65, and prevalence soars later in life
- Expected to become a worldwide epidemic as populations age
- Most cases are terminal illnesses
- Alzheimer's Disease is the most common, but **mixed** types often occur (especially in late life)
- Each type of dementia differs in terms of pathophysiology

Common Dementia Syndromes

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- Alzheimer's Disease (AD)
- Vascular Disease (VD)
- Lewy Body Disease (LBD)
- Parkinson’s Disease Dementia (PDD)
- Frontotemporal Disease (FTD)

Behavioral and Psychological Symptoms of Dementia (BPSD)

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- Also known as "neuropsychiatric symptoms" of dementia:
  - Agitation, anger, aggression, psychosis, depression, apathy, anxiety, disinhibition, sleep disturbance, appetite change, etc.
- Difficult to categorize, which creates problems with research and treatment
- Some behaviors may be related to specific regions of the brain, certain neurotransmitters, or selected neural circuits
- Better biomarkers needed

BPSD

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- Very common in dementia (97% 5 yr prevalence)
- Tend to be episodic and change over time
- Much more common in LTC settings than community settings
- Pain and boredom are common causes
  - Preuss, 2016

BPSD

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- Sometimes can be first sign of the disease process
- Depression/apathy common early and agitation/psychosis common later as diseases progress
- BPSD occurs at different frequencies in different dementia syndromes:
  - Depression more common in VD
  - Visual hallucinations more common in LBD
  - Disinhibition more common in FTD

    - Kwon, 2024

BPSD Consequences

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- Earlier nursing home placement
- Increased hospital admissions
- More rapid progression of illness
- Increased mortality and morbidity
- Increased restraint use
- Increased cost of care
- Caregivers suffer in terms of health, income, quality of life

- Preuss 2016

BPSD Frequencies (All dementia types)

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- **Agitation**: 38-64%
  - Walking aimlessly: 0-50%
  - Pacing: 26-48%
  - Restlessness: 22-27%
  - Resistance: 27-65%
  - Verbal aggression: 11-61%
  - Physical aggression: 0-46%
- **Psychosis**
  - Hallucinations: 17-24%
  - Delusions: 33-40%
- **Depression**: 54-64%
- **Apathy**: 33-63%
- **Sleep problems**: 0-47%

- Pruess, 2016

Assessing BPSD

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- Prior history of mental illness
- Premorbid personality and behavior
- Time frame, patterns, triggers
- Environment
- Unmet needs
- Changes in medical status (Pain, metabolic, dehydration, infection)
- Caregivers may need to become detectives

Non-pharmacological interventions for BPSD

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- **Most experts believe that this should be the initial intervention**

- But many barriers exist:
  - Lack of provider training
  - Lack of research on interventions
  - More time consuming (results not rapid)
  - Lack of staff
  - Lack of equipment
  - Staff attitudes/expectations

- Mageirski, 2020

Non-pharmacological interventions for BPSD

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- Research/evidence is somewhat limited
- **Music**, exercise, animals, dolls, art, acupuncture, aroma, Snozelen, simulated presence, validation, reminiscence, bright light, breath of fresh air, virtual reality, robots, video gaming, computers, dance, gardening
- Alter environment
- Modify approaches
- Create structure and routine
- Identify and satisfy unmet needs
- Be patient-centered
- Caregiver education and support is important (must buy in)

When Should Pharmacological Interventions be Used?

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- Non-pharmacological interventions failed
- Severe behaviors
- Imminent danger to self/others
- Need quick results

Pharmacological Treatment of Specific BPSD

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- All medications are off-label (except brexpiprazole)

Agitation

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- Difficult to define, which also makes it difficult to study
- Common, especially in later stages
- Can be very disruptive and cause safety concerns
- May include: Irritability, yelling, physical aggression, pacing, restlessness, fidgeting, hand wringing, abnormal motor activity, emotional distress, wandering, exit seeking, hostility, anger

Agitation: Pharmacological Treatment

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- Antipsychotics:
  - **Brexpiprazole**>Risperidone>aripiprazole>olanzapine>quetiapine
- Antidepressants:
  - SSRIs: **Citalopram**, sertraline, fluoxetine
  - Trazodone
  - Mirtazapine
- Carbamazepine
- Gabapentin
- Prazosin

Antipsychotics

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- Brexpiprazole
- Risperidone
- Aripiprazole
- Olanzapine
- Quetiapine
- Haloperidol
- Pimavanserin
- Clozapine
- Others

Antipsychotics

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- Probably the most effective treatments currently available for severe BPSD
- Although tranquilization may be immediate, antipsychotic action may take weeks
- Initial trial of 4 weeks, reassess every 1-3 months, attempt discontinuation after 4 months
- Long-acting injectable only for premorbid severe mental illness

Higher Mortality Related to Antipsychotics Use in Dementia

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- Typical antipsychotics have higher mortality rates than atypical (26-30% higher)
- Quetiapine may be a lower risk than other antipsychotics
- Mortality rate highest early in treatment and then become lower later
- Mortality rates are increased at higher doses
- Causes of death include cerebrovascular disease, infections, pneumonia, cardiovascular disease, falls

- Masopust 2018

Brexpiprazole

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- “Dopamine stabilization” mechanism (agonist and antagonist)
- FDA approved for agitation in Alzheimer’s
- Not effective as PRN
- Not indicated for psychosis
- Expensive
- Titrate up to 2 mg q day

Risperidone

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- Fair evidence for agitation and psychosis
- Approved in other countries (with strict criteria)
  - Fail non-pharm, severe agitation/aggression, time limit
- Available in liquid or ODT
- Adverse effects: Orthostasis, elevated prolactin, EPS
- Start with 0.25-0.5 mg q HS

Aripiprazole

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- Fair evidence for agitation and psychosis
- Dopamine stabilization similar to brexpiprazole
- No QT prolongation
- Not appropriate for PRN
- Start with 2.5 mg q day

Olanzapine

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- Some evidence for agitation and psychosis
- Adverse effects: Metabolic, anticholinergic
- Available in rapidly-acting injectable or ODT
- Start with 2.5-5 mg q HS

Quetiapine

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- Weak evidence for agitation and psychosis
- May be better tolerated (low EPS)
- Relatively rapid onset
- May be anxiolytic
- Sedating
- Start with 25 mg q HS (or split dose)

Haloperidol

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- Some evidence for agitation and psychosis
- First generation (typical) antipsychotic
- Available in liquid or rapidly-acting injection
- Adverse effects: EPS, anticholinergic, QT prolongation
- Risks often outweigh benefits
- Avoid in Parkinsonian syndromes (NMS)
- Best suited for emergencies where rapid tranquilization needed
- 2.5-5 mg IM (twice as bioavailable)

Pimavanserin

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- Serotonin agonist with very little dopaminergic activity
- Indicated for psychosis related to Parkinson's Disease
  - Not indicated for other uses
- Minimal adverse effects
- 34 mg q day

Clozapine

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- No evidence for agitation
- Reasonable choice for severe psychosis in PDD or LBD
- Very low risk of EPS
- Complex to manage
- Must order CBCs periodically (agranulocytosis)
- Many possible adverse effects including metabolic, sedation, anticholinergic, seizure, myocarditis
- Start with 25 mg q HS and titrate up

Antidepressants

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- Good starting point, especially if mood symptoms present such as irritability, anger, anxiety, depression, etc.
- Start low and go slow to avoid paradoxical agitation/anxiety
- SSRIs
- Trazodone
- Mirtazapine
- SNRIs
- Avoid TCAs

Citalopram

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- Fair evidence for agitation
- May even be as beneficial as antipsychotics for agitation or psychosis
- QT prolongation (esp. at doses >20 mg in elderly)
- Start at 5-10 mg q am
- Escitalopram probably similar but different dosing

Sertraline

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- Minimal evidence for agitation
- But relatively few interactions or adverse effects
- Start at 12.5-25 mg q am

Fluoxetine

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- Very little evidence for agitation
- But long half-life and dosing options may make it appealing, especially for non-adherent patients
- Start at 5-10 mg q am

Trazodone

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- Some evidence to use in small doses to reduce agitation or anxiety (PRN or scheduled)
- Not a rapid onset of action
- Be aware of potential cardiac issues
- Dosing is variable
- Start at 12.5-25 mg doses (PRN or scheduled)

Mirtazapine

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- Minimal evidence
- Consider if irritable, anxious, depressed, insomnia, anorexia
- Start at 3.75-7.5 mg q HS

Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)

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- Very little evidence for agitation
- Venlafaxine, duloxetine, etc.
- Consider if pain is an issue

Anticonvulsants

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- For agitation, aggression, mania:

  - Carbamazepine
  - Divalproex
  - Gabapentin

Carbamazepine

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- Some evidence for agitation, aggression, hostility
- Also for mania
- Monitor LFTs and CBC (blood dyscrasias), and serum level
- Can cause induction of metabolism which reduces levels of some other drugs
- Does not usually cause weight gain or sedation
- Start at 100 mg TID

Gabapentin

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- Minimal evidence for agitation
- Consider if anxiety, insomnia or pain
- Bypasses liver
- Dosing is variable
- Start at 100 mg tid

Divalproex

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- Weak evidence for agitation, aggression
- Could be an option for mania
- Monitor LFTs, CBC, NH4, serum level
- Sprinkles or liquid may improve adherence
- Adverse effects: Sedation, confusion, falls, hair loss
- Mortality risk may be similar to antipsychotics
- Start at 250-375 mg BID

Prazosin

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- Minimal evidence for agitation
- Alpha-1 blocker
- Sometimes used for nightmares in PTSD
- Monitor blood pressure
- Start at 1 mg q day and titrate as high as 6 mg q day

Benzodiazepines

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- Lorazepam, alprazolam, clonazepam, diazepam, etc.
- Widely used in dementia, but very little evidence to support efficacy
- Adverse effects: Sedation, falls, confusion, dependence, paradoxical disinhibition
- Best utilized for high anxiety or catastrophic events (IM) when rapid results needed
- Avoid in delirium (except alcohol related)

Antihistamines

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- Hydroxyzine
- Diphenhydramine
- Common in OTC sleep meds
- Adverse effects: Anticholinergic, confusion, sedation
- Should be avoided in most cases

Cholinesterase Inhibitors and Memantine

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- Weak evidence for agitation
- If BPSD occurring, avoid discontinuation
- Rivastigmine and donepezil may be useful for psychosis in LBD

Psychosis

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- **Delusions**
  - Infidelity, theft, harm
  - Differentiate from disorientation
- **Hallucinations**
  - Visual (people, animals) or auditory (voices)
- **Misidentification**
  - Capgras, strangers in house, TV images real, mirror image not real

- Often driven by circumstances around them
- Especially common in LBD (75%)
- Uncommon in FTD

- Cummings, 2024

Psychosis: Treatment

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- Atypical antipsychotics
  - Risperidone>aripiprazole>olanzapine>quetiapine
- If associated with LBD:
  - Rivastigmine, donepezil, quetiapine or clozapine
- If associated with PDD:
  - First lower dopaminergic drugs
  - Then can try pimavanserin, quetiapine or clozapine

Depression

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- Common, especially in early stages
- Unclear whether it is a risk factor for dementia or a sign of impending dementia
- Treatment: SSRI, SNRI

Apathy

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- Very common (esp in FTD), but treatment options limited
- May be difficult to differentiate from depression
- Associated with many negative outcomes
- No effective treatments known, but could try methylphenidate, cholinesterase inhibitors, SSRI

Anxiety

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- Avoid benzodiazepines, antihistamines and antipsychotics
- Use SSRI, SNRI, buspirone
- Non-pharm interventions may help as well

Sleep

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- Wide variety of sleep disturbances (different for each dementia syndrome)
- Sleep patterns often erratic and disrupted causing caregiver stress
- Minimal evidence, but can try melatonin, ramelteon, trazodone, suvorexant (orexin blocker)
- Avoid benzodiazepines, Z-drugs and antihistamines
  - Except REM sleep behavior disorder in LBD

Disinhibition

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- Inability to self-regulate impulses
- May result in socially inappropriate speaking, touching, intrusion, lack of decorum, theft, excessive spending, driving erratically, conflicts, etc.
- Sexually inappropriate behavior is closely related
- Difficult to treat
- No effective medications known, but could try SSRI, antipsychotic, anticonvulsant, methylphenidate
- If PDD, try lowering dopaminergic drugs

Sexually Inappropriate Behavior

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- Statements, actions, touching, exposing
- Mostly in males
- Factors: Lack of partner, misinterpretation of social cues, lack of privacy, environmental stimulation
- Must know pre-morbid behavior
- Caregiver education is important

- Sarangi, 2021

Sexually Inappropriate Behavior: Treatment

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- Non-pharm: Distract, divert, keep hands engaged
- Caregiver education important
- SSRI/SNRI>Atypical antipsychotics>hormonal
- Antidepressants are considered frontline pharmacological treatment, but hormonal treatments tend to be more effective and have more rapid response
  - Antidep/antipsy remission 55%, hormonal remission 95%
- If manic, utilize mood stabilizers or antipsychotics
- If PDD, try lowering dopaminergic drugs

- Lane, 2025

Hormonal Treatments

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- Medroxyprogesterone acetate
  - Adverse effects: Weight gain, thromboembolic risk, mood changes
  - Usually no feminization
  - 150 mg IM q 2wk
- Others: Estrogen, cyproterone, finasteride, etc.
- Some experts see an ethical dilemma associated with hormonal treatment, so full informed consent is critical

Interventional Treatments

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- Electroconvulsive therapy (ECT)
- Transcranial magnetic stimulation (TMS)

Major Neurocognitive Disorder Due to Traumatic Brain Injury

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- Different clinical features and treatment
- Doesn't progress over time, but higher risk for dementia later
- Propranolol, divalproex, carbamazepine, antipsychotics
- Avoid benzodiazepines

  - Williamson, 2019

Delirium

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- Temporary state of increased confusion due to underlying acute medical issue
- Dementia is a risk factor
- Can be hypoactive or hyperactive
- Identify and treat underlying problem
- If severe agitation or psychosis occurs, may use antipsychotics (haloperidol, quetiapine, etc.)
- Avoid benzodiazepines (unless alcohol related)

Psychopharmacological Treatment in Long-Term Care

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- Regulated by federal guidelines that are enforced by state surveyors (DIAL)
- Pharmacy consultants review regimens in order to improve compliance
- Antipsychotics and sedative-hypnotics are especially scrutinized (particularly in dementia patients)
- Gradual dosage reductions and non-pharmacologic interventions strongly encouraged
- PRN use highly regulated (duration, assessment, documentation)

The PRN Culture in Facilities

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- Options for PRN treatment of BPSD very limited
- Many of existing options have serious adverse effects
- Doctors and nurses trained to solve problems; often focused on treating symptoms rather than preventing them
- Better to be pro-active by modifying scheduled doses

PRN Options

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- **Trazodone**
- Lorazepam (drops, tab, IM)
- Alprazolam
- Quetiapine
- Haloperidol IM
- Olanzapine IM
- Hydroxyzine

Improving Adherence

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- Explore timing, swallowing and other issues with caregivers
- Consider frequency of dosing, number of pills, type of pills, ODT, crushable, liquid, injectable, etc.
- May conceal if decision maker agrees

Higher Level of Care For More Complex Patients

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- **It doesn't exist!**
- Very difficult to find inpatient care for dementia-related behaviors
- Often boarded in ED, heavily medicated, and sent back

Being Studied

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- Dextromethorphan/bupropion (major depression-rapid)
- Dextromethorphan/quinidine (pseudobulbar affect)
- Dexmedetomidine (PRN agitation in schizophrenia/bipolar)
- Xanomeline/trospium (schizophrenia-muscarinic)
- Cannabinoids:
  - Nabilone (pain)
  - Dronabinol (appetite)

Summary Points

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- Almost all dementia patients will have BPSD during the course of their illness, and these symptoms have serious consequences for the patients and caregivers
- Each dementia syndrome is different in terms of underlying pathophysiology and the types of neuropsychiatric symptoms they experience
- Therefore, one size doesn't fit all and each patient should be treated individually according to their clinical presentation
- This can best be accomplished by a careful assessment of the medical facts and their behaviors
- The first priority should be to "do no harm" and avoid medications that could potentially have adverse effects
- Be proactive instead of reactive
- Equip caregivers with the tools needed to manage these behaviors in order to reduce reliance on medication

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