Dementia-Related Psychosis in Long-Term Care: Identification and Management

Faculty
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University of Buffalo School of Pharmacy and Pharmaceutical Sciences

Nearly 50 million people worldwide live with dementia, and of those, up to 90% will experience Behavioral and Psychological Symptoms of Dementia (BPSD), including psychosis, during their disease progression. Psychotic symptoms of dementia include hallucinations, delusions, and delusional misidentifications. These symptoms decrease patients’ quality of life and are often distressing for patients and caregivers. Management of psychosis in dementia can be challenging and requires a comprehensive pharmacologic and non-pharmacologic approach. Pharmacologic management is complicated by a lack of approved medications for this indication and marked by low efficacy and high risk of adverse effects for the agents normally employed. This educational activity will educate pharmacists and nurses on the types and causes of dementia-related psychosis (DRP) and how to recognize DRP in the older adult population. This activity will educate pharmacists and nurses on the proper use of treatments for DRP, with a focus on the long-term care setting. This activity will also include discussion on emerging treatments for DRP, as this remains an area of high need. Clinical data about agents currently being studied for DRP will be presented and discussed to give learners the most up-to-date view of the treatment landscape.

Learning Objectives

Pharmacist
1. Differentiate between types and causes of dementia-related psychosis (DRP).
2. Compare and contrast treatments for DRP, including non-pharmacological and current pharmacological treatments.
3. Examine clinical data for agents being studied for the treatment of DRP.

Nurse
1. Differentiate between types and causes of dementia-related psychosis (DRP).
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Target Audience
Pharmacists, Nurses

Universal Activity Number

Pharmacist 0798-0000-21-029-L01-P
Nurse 0798-0000-21-029-L01-N

Credit Hours 1.0 Hour
Activity Type Application-Based
CE Broker Tracking Number 20-770213

Activity Release Date May 18, 2021
Activity Offline Date May 18, 2024
ACPE Expiration Date May 18, 2024

Educational Support Provided By
Acadia Pharmaceuticals, Inc.

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Program Overview

Nearly 50 million people worldwide live with dementia, and of those, up to 90% will experience Behavioral and Psychological Symptoms of Dementia (BPSD), including psychosis, during their disease progression.

Psychotic symptoms of dementia include hallucinations, delusions, and delusional misidentifications. These symptoms decrease patients’ quality of life and are often distressing for patients and caregivers.

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Clinical data about agents currently being studied for DRP will be presented and discussed to give learners the most up-to-date view of the treatment landscape.

Learning Objectives

At the conclusion of this activity, participants should be better able to:

• Differentiate between types and causes of dementia-related psychosis (DRP)

• Compare and contrast treatments for DRP, including non-pharmacological and current pharmacological treatments

• Examine clinical data for agents being studied for the treatment of DRP.

Meet Our Patient

• JT is a 75-year-old male who developed Parkinson’s disease (PD) approximately 15 years ago, with motor difficulties which started with tremors roughly 5 years after his diagnosis.

• Although JT did not have a significant medical history prior to his PD diagnosis, he struggled with metabolic risks that included elevated blood glucose, pre-hypertension and high cholesterol.
Meet Our Patient

Because he was also considered moderately obese, JT’s medical physician had repeatedly educated him on the need to lose weight and focus on lifestyle factors to improve his health.

JT’s wife reported a change in JT’s memory just before his PD tremor became noticeable. He became more forgetful and had trouble finding words. At that time, these symptoms were dismissed as potential neurologic effects of the PD.

Years later, as these behavioral and memory symptoms worsened, a CT scan determined JT likely experienced a small unnoticed stroke that resulted in vascular dementia years later.

Even though they had no pets. JT’s wife had also noticed recently that he started describing seeing black cats running around the house, even though they had no pets.

He also began exhibiting paranoia and asking her where she had “been” even though she had not left the house and had been caring for him all day. He became more aggressive, and she admitted to feeling afraid for her safety and reluctantly agreed with family and friends to admit JT to a long-term care facility for treatment.

Dementia-Related Psychosis in Long-Term Care: Identification and Management

Objective #1

Differentiate between types and causes of dementia-related psychosis (DRP)

Dementia Overview

- Dementia is a general term that describes loss of problem solving and thinking capabilities (including memory)
- Affects mostly older adults and is not a “normal” part of aging
- Estimated 5 million adults with dementia in 2014 and projected to be ~14 million by 2060
- Normal aging may include some age-related memory changes that may show as:
  - Occasionally misplacing car keys
  - Struggling to find a word but remembering it later
  - Forgetting the name of an acquaintance
  - Forgetting the most recent events
- Changes associated with normal aging can occur but allow knowledge and experiences built over one’s lifetime, including old memories and language to stay intact.

Different Causes of Dementia

What increases the risk for dementia?

- **Age:** the strongest known risk factor for dementia is increasing age, with most cases affecting those of 65 years and older
- **Family history:** those who have parents or siblings with dementia are more likely to develop dementia themselves
- **Race/ethnicity:** older black individuals are twice more likely and Hispanic individuals are reported to be 1.5 times more likely to have dementia than white individuals
- **Poor heart health:** high blood pressure, high cholesterol, and smoking increase the risk of dementia if not managed properly
- **Traumatic brain injury:** head injuries can increase the risk of dementia, especially if they are severe or occur repeatedly

Different Types of Dementia

- **DSM-5** is the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders
- Dementia, amnestic, and cognitive disorders included as neurocognitive disorders (NCDs)
- NCDs are considered either mild or major and cover a wide array of diagnoses
- Behavioral and psychological symptoms of dementia (BPSD) occur in approximately 90%
- BPSD lead to increased caregiver burden and early unnecessary institutionalization.
- Most patients with dementia will experience one or more BPSD's
Different Types of Dementia

Alzheimer’s disease (AD)
- Most common cause of dementia, accounting for 60%-80% of cases
- First-degree relative with AD increases the risk of developing it by 10%-30%

Vascular dementia (VD)
- About 10% of dementia cases are linked to VD
- Diabetes, high blood pressure, and high cholesterol are also risk factors.
- Symptoms vary depending on the area and size of the brain impacted. The disease progresses with symptoms worsening with additional strokes

Dementia with Lewy bodies (DLB)
- In addition to memory loss, movement or balance problems and altered alertness including daytime sleepiness, confusion, or staring spells. Accounts for up to 7% of dementia cases
- Commonly experience trouble sleeping at night or may experience visual hallucinations

Symptom Clusters of Dementia

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<tr>
<th>Symptom</th>
<th>Prevalence</th>
<th>Cluster</th>
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<td>Agitation/aggression</td>
<td>22-52%</td>
<td>Hyperactivity</td>
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<td>Depression</td>
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<td>Psychosis</td>
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Differentiate Between Types and Causes of Dementia-Related Psychosis (DRP)

- Progression of BPSD and DRP is highly individualized and differs based on the type of dementia
- According to Li and colleagues, consider the possibility of early-onset AD in middle-aged or elderly patients whose first symptoms are the behavioral and psychological symptoms of dementia
- Patients with early-onset AD that exhibits first as psychotic symptoms usually lack obvious cognitive impairment, so they may be misdiagnosed with late-onset schizophrenia
- To distinguish early-onset AD from late-onset schizophrenia, clinicians should evaluate cognitive function, perform MRI and PET

Frontotemporal dementia (FTD)
- Often leads to changes in personality and behavior because of the part of the brain it affects. There may also be problems with language skills like speaking or understanding.
- Mixed dementia
  - It is estimated that 50% of the NCD population has mixed dementia (both an AD and VD presentation). Disease progression may be faster than with one kind of dementia.
- Reversible causes
  - People who have dementia may have a reversible underlying cause such as side effect of medication, increased pressure in the brain, vitamin deficiency, and thyroid hormone imbalance.
- Other causes: traumatic brain injury, HIV infection, prion disease (e.g., mad cow disease), Parkinson’s disease, or Huntington’s disease

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Differentiate Between Types and Causes of Dementia-Related Psychosis (DRP)

- The prevalence of hallucinations and delusions in dementia is generally progressive and often may double over the course of the illness
- Brandt and colleagues conducted a quantitative online survey which was patient reported (completed by patients with dementia-related psychosis) or care partner reported (by care partners of patients with dementia-related psychosis)
- Subjects were recruited through direct outreach by the advocacy groups UsAgainstAlzheimer’s and the Lewy Body Dementia Association
- In total, 26 patients and 186 care partners participated in the quantitative online survey
Differentiate Between Types and Causes of Dementia-Related Psychosis (DRP)

• The dementia-related psychosis symptoms most frequently reported in patients:

<table>
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<th>Experienced by the patient</th>
<th>Reported by caregivers</th>
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<td>Visual hallucinations (88.5%)</td>
<td>paranoid delusions (75.8%)</td>
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<tr>
<td>auditory hallucinations (53.8%)</td>
<td>visual hallucinations (75.3%)</td>
</tr>
<tr>
<td>distortion of senses (53.8%)</td>
<td>lack of trust for loved ones (52.2%)</td>
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• Visual hallucinations were reported to occur in roughly 50% of patients at least weekly.

Symptom Clusters of Dementia

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<td>Apathy</td>
<td>29-76%</td>
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Objective #2

Compare and contrast treatments for DRP, including non-pharmacological and current pharmacological treatments

Symptom Clusters of Dementia

- Recommendation against using sleep promoting medications, including melatonin, for older adults with Irregular Sleep-Wake Rhythm Disorder (ISWRD) and a comorbid diagnosis of dementia
- The authors concluded that withdrawn behaviors observed in patients during melatonin administration, may be related to supraphysiologic serum concentrations
- 2.5 mg dose administered during the study that led to sleepiness and dysphoria which was misinterpreted as mood change

Compare and Contrast Treatments for DRP, Including Non-Pharmacological and Current Pharmacological Treatments: Psychosocial Interventions

The Association recommends training and education for both professional and family caregivers on psychosocial interventions that might include:
- Review medications, especially new medications
- Promote routine activity
- Separate the person from what seems to be upsetting them
- Assess for the presence of pain, constipation, or other physical problem
- Travel with them to where they are in time
- Don’t disagree; respect the person’s thoughts even if incorrect. Avoid finger-pointing, scolding, or threatening

Compare and Contrast Treatments for DRP: When Considering Pharmacological Treatment Interventions

- Only after initiating non-pharmacologic alternatives as first-line therapy for control
- Identify and remove triggers for BPSD
- Assess severity and consequences of BPSD with less severe behaviors (limited harm) with more severe or “high risk” behaviors
- Determine overall risk to self or others and risks and benefits with and without medication
- Consider pharmacotherapy as a short-term intervention that must be regularly reevaluated for appropriate time of cessation or need for continuation

Compare and Contrast Treatments for DRP: When Considering Pharmacological Treatment Interventions

- In recent years, several pharmacological and psychosocial approaches have proven inadequate
- **Medication with benefits when risks are managed**: antipsychotics, AChEIs, NMDA antagonist, and antidepressants
- **Medication with a risk greater than potential benefit**: benzodiazepines, AED mood stabilizers associated with high probability of adverse effects and low probability of meaningful clinical improvement
### Compare and Contrast Treatments for DRP, Including Non-Pharmacological and Current Pharmacological Treatments: Antipsychotics

- **Target symptoms:** severe agitation, aggression and psychosis
- **Benefits:** small to moderate efficacy with onset generally observed within the first 1 to 2 weeks of use (however sedating effects are usually reported upon immediate administration)
- **Risks:** in addition to the increased risk of mortality:
  - Extrapyramidal side effects (EPS)
  - Metabolic consequences
  - Risk of thromboembolism
  - Potential increased cognitive decline
  - Risk of falls
- **Stool off label use in DRP**
- **Risperidone** is indicated for the short-term treatment (6–12 weeks) of persistent agitation in AD in some countries outside the US.

### Compare and Contrast Treatments for DRP, Including Non-Pharmacological and Current Pharmacological Treatments: Acetylcholinesterase Inhibitors (AChEIs)

- **Medication:** donepezil (Aricept), galantamine (Razadyne), rivastigmine (Exelon)
- **Target symptoms:** depression, dysphoria and anxiety
- **Benefits:** small improvements in BPSD, evidence of slowed cognitive decline (disease progression remains inevitable).
- **Risks:** in addition to GI complaints:
  - Anorexia and weight loss
  - Bradycardia
  - Risk of falls

### Compare and Contrast Treatments for DRP, Including Non-Pharmacological and Current Pharmacological Treatments: Antidepressants

- **Medication:** selective serotonin reuptake inhibitors (SSRIs) - sertraline (Zoloft), citalopram (Celexa) and escitalopram (Lexapro)
- **Target symptoms:** agitation, depression and irritability
- **Benefits:** tolerability reported to be better than antipsychotics, and can have similar efficacy for target symptoms
- **Risks:** in addition to GI complaints:
  - Hypotension
  - Increased bleeding potential
  - Possible bone loss
  - Tremor/akathisia
  - Cognitive decline

### Compare and Contrast Treatments for DRP, Including Non-Pharmacological and Current Pharmacological Treatments: NMMA Antagonist Memantine

- **Medication:** N-methyl-D-aspartate (NMDA antagonist) Memantine (Namenda) approved for the treatment of AD, has some effects on behavior as measured by the Neuropsychiatric Inventory (NPI)
- **Target symptoms:** agitation, aggression and delusions
- **Benefits:** small improvements in BPSD and slowed cognitive decline (progression continues)
- **Risks:** minimal adverse effects reported but include:
  - Headache
  - Dizziness
  - Constipation
  - Reduced agitation and irritability were seen with the add-on of memantine to AChEi
  - Dementia drugs should not be considered as primary therapy for agitation in AD; however, they should not be discontinued unless there is clear evidence that their introduction may have caused the episode

### Compare and Contrast Treatments for DRP, Including Non-Pharmacological and Current Pharmacological Treatments: Regulations and Recommendations

- **Regulatory expectations**
- **Gradual dose reductions**
- **Chemical restraint and ethical considerations**
When a resident is experiencing an acute medical problem or psychiatric emergency that poses an immediate risk to self or others, treatment should be initiated immediately. However, use should only be initiated/used in the presence of active clinical symptoms and following nonpharmacological interventions and least restrictive measures have been attempted.

### Limiting PRN Psychotropic Orders

- **November 28, 2017, CMS announced several regulatory changes for skilled nursing facilities:**
  - Any drug that affects brain activities associated with mental processes and behavior
  - These drugs include antipsychotics, antidepressants, antianxiety medications, hypnotics, as well as medication classes that may affect brain activity which are now included on expanded list
  - This expanded list of psychotropic medications includes central nervous system agents, mood stabilizers, anticonvulsants, muscle relaxants, anticholinergic medications, antihistamines, N-methyl-D-aspartate receptor modulators, and over-the-counter natural or herbal products.

- The definition of a psychotropic medication now includes:
  - NMDA modulators, and over-the-counter natural or herbal products.

- The rules regarding extension of PRN antipsychotics are even more stringent:
  - Prescriber must directly examine and assess the resident and document clinical rationale for the extension, which includes the expected benefit specifically for that patient.
  - This documentation is required every 14 days for a resident receiving a PRN antipsychotic without exception, including hospice patients.

- Limiting PRN antipsychotic orders to 14 days and not entering a new order without evaluating the resident.

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- Any drug that affect...
Examine Clinical Data for Agents Being Studied for the Treatment of DRP

- New drug candidates target a different pathology than that known to cause dementia-related psychosis but are associated with a favorable pharmacologic profile and benefit
- These include agonists of M1/M4, CB1, and mGluR2
- Future pharmacotherapy of dementia related psychosis, agitation, and aggression will depend on outcomes of phase III trials and future approvals of novel agents or old agents “drafted” for new use
- Researchers now suggest that avoiding antagonism of the H1, M1, and alpha-2 adrenergic receptors to reduce the risk of stroke, excessive sedation, cardiotoxicity and additional worsening memory impairments

Clinical Data for Agents Being Studied for Treatment of DRP

<table>
<thead>
<tr>
<th>Phase of trial</th>
<th>Duration</th>
<th>Subjects</th>
<th>Dose</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase II</td>
<td>36 weeks</td>
<td>N=360</td>
<td>20 mg or 34 mg once daily</td>
<td>N=360 DRP</td>
</tr>
<tr>
<td>Clinical trial: NCT0325556</td>
<td>12 weeks</td>
<td>AD</td>
<td>34 mg once daily</td>
<td>Large treatment effects in AD patients with more severe psychosis at baseline (NPI-PS 5-7)</td>
</tr>
<tr>
<td></td>
<td>12 weeks</td>
<td>Open-label + 26 weeks Double-blind period</td>
<td>on their open-label phase</td>
<td>A long-term relapse prevention study of pimavanserin for the treatment of hallucinations and delusions associated with DRP</td>
</tr>
</tbody>
</table>

Examine Clinical Data for Agents Being Studied for the Treatment of DRP

- The dysfunction of the serotonin (5-HT2A) receptor has been associated with onset of psychosis and aggression in AD
- Pimavanserin (Nuplazid) is a selective 5-HT2A inverse agonist (phase III clinical trials)
- Other second-generation antipsychotics (SGAs) that also act S-HT2A antagonists: lumateperone (Cyp�ix) and brexipiprazole (Rekulti) also advanced to phase III clinical trials for dementia related psychosis and agitation
- Brexipiprazole was reported to significantly reduce agitation; lumateperone trial was terminated due to lack of efficacy
- Pimavanserin has been a target of ongoing FDA review for potential expansion of indication to include DRP

Examine Clinical Data for Agents Being Studied for the Treatment of DRP

- The international Delphi consensus published 2019
- Expert panel comprised of 11 international members with clinical and research expertise in BPSD management
- Consensus outcomes showed a clear preference for an escalating approach to the management of BPSD commencing with the identification of underlying causes
- Based on relevant results observed in the phase II and phase III clinical trials and evidence of efficacy and tolerability of this drug in PDP patients with cognitive impairment
- Regarding future treatments for psychosis, the greatest priority was placed on pimavanserin

Examine Clinical Data for Agents Being Studied for the Treatment of DRP

- New drug candidates target a different pathology than that known to cause dementia-related psychosis but are associated with a favorable pharmacologic profile and benefit
- These include agonists of NMDA, M1/M4, S-HT2A, CB1, and mGluR2 receptors with a variety of agents having progressed to advanced preclinical development

Examine Clinical Data for Agents Being Studied for the Treatment of DRP

- NMDA (Indirect) SND-51-advanced to phase II clinical trials to evaluate safety and efficacy in the treatment of dementia and psychosis
- mGluR2 Intra-Cellular Therapies Inc.
- Brexpiprazole (BMS-855835) advanced to phase II clinical trials to evaluate safety and efficacy in the treatment of dementia and psychosis
- Pimavanserin (Nuplazid) advanced to phase III clinical trials to evaluate safety and efficacy in the treatment of agitation and psychosis in Alzheimer’s disease
- Lumateperone (Cyp�ix) advanced to phase III clinical trials for dementia-related psychosis and agitation
- Brexipiprazole (Rekulti) advanced to phase III clinical trials for dementia-related psychosis and agitation
Thank You
References


Clinical Trials:

- A Phase 3, 12-week, Multicenter, Randomized, Double-blind, Placebo-controlled Trial to Evaluate the Efficacy, Safety, and Tolerability of Brexpiprazole in the Treatment of Alzheimer's Agitation - Full Text View - ClinicalTrials.gov
- Safety and Tolerability Study of Flexible Dosing of Brexpiprazole in the Treatment of Subjects With Agitation Associated With Dementia of the Alzheimer's Type - Full Text View - ClinicalTrials.gov
- Brexpiprazole for the Long-term Treatment of Patients With Agitation Associated With Dementia of the Alzheimer's Type - Full Text View - ClinicalTrials.gov
- A 12-week Extension Study to Evaluate the Safety and Tolerability of Brexpiprazole in the Treatment of Patients With Agitation Associated With Dementia of the Alzheimer's Type - Full Text View - ClinicalTrials.gov
- Brexpiprazole for the Treatment of Patients With Agitation Associated With Dementia of the Alzheimer’s Type - Full Text View - ClinicalTrials.gov
- Relapse Prevention Study of Pimavanserin in Dementia-related Psychosis - Full Text View - ClinicalTrials.gov