Pharmacologic Management of the Behavioral and Psychological Symptoms of Dementia

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Objectives

• Identify behavioral disturbances commonly experienced by elderly patients with dementia
• Identify medical causes of behavioral disturbances in the elderly
• Evaluate the efficacy of pharmacologic treatments in improving behavioral and psychological symptoms of dementia
• Recognize risk vs benefit of medications used to manage the behavioral and psychological symptoms of dementia
Behavioral and Psychological Symptoms of Dementia (BPSD)

• Definition:
  • Heterogeneous range of psychological reactions, psychiatric symptoms, and behaviors that are unsafe, disruptive, and impairs the care of the patient in a given environment
Behavioral and Psychological Symptoms of Dementia (BPSD)

- Prevalence
  - ~30% of community-dwelling
  - ~80% in LTC
## BPSD Clusters

<table>
<thead>
<tr>
<th>Cluster</th>
<th>Symptom</th>
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</thead>
<tbody>
<tr>
<td>Depression</td>
<td>Sadness, tearfulness, hopelessness, low self esteem, anxiety guilt</td>
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<tr>
<td>Apathy</td>
<td>Withdrawal, anhedonia</td>
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<tr>
<td>Aggression</td>
<td>Aggressive resistance, physical or verbal aggression</td>
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<tr>
<td>Psychomotor agitation</td>
<td>Aimless walking, pacing, shadowing, restlessness, repetitive actions, dressing/undressing, sleep disturbances</td>
</tr>
<tr>
<td>Psychosis</td>
<td>Hallucinations, delusions, misidentification</td>
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</tbody>
</table>
Reversible Medical Causes

- Acute Infection
- Delirium
- Dehydration
- Hypoxia
- Pain
- Medication side effects
  - Anticholinergic
  - Benzodiazepines
Standardized Rating Scales

- **Neuropsychiatric Inventory (NPI)**
  - Scale assesses behavioral problems in dementia
  - Scores range from 10 (least frequent) to 144 (most frequent)

- **Behavioral Pathology in Alzheimer’s Disease (BEHAVE-AD)**
  - Designed to assess behavioral symptoms and measure outcomes in treatment studies
  - Scores can range from 0 to 78. The higher the number, the more significant the behaviors
Non-pharmacological Interventions

- Large scale RCTs are scarce
- Limited studies have suggested that implementation and education of non-pharmacological interventions reduces psychotropic drug use
- Target three broad problematic behaviors:
  1. Behaviors caused by unmet patient needs
  2. Behaviors caused by aggravating factors
  3. Behaviors caused by ill-suited environments
- Intervention types include:
  - Sensory stimulation
  - Social contact
  - Environment
  - Orientation
  - Recreation
  - Cognitive Behavioral Therapy and Cognitive Stimulation Therapy
Pharmacologic Agents

• Antipsychotics
• Antidepressants
• Benzodiazepines
• Anticonvulsants
• Cholinesterase inhibitors
• Memantine
• Miscellaneous agents
Antipsychotics
Antipsychotics

• Most studied class in the treatment of BPSD
  • More than 37 trials
    • Three Spectrums
      • Psychosis
      • Agitation
      • Overall BPSD
  • Most Studied
    • Risperidone (Risperdal®)
    • Olanzapine (Zyprexa®)
    • Quetiapine (Seroquel®)
    • Aripiprazole (Abilify®)
Risperidone
(Risperdal®)

- 8 trials
- Dose: 0.5 mg to 2.5 mg
- Only drug to demonstrate a high level of efficacy across the three spectrums of BPSD
- Considered the antipsychotic of choice
Olanzapine (Zyprexa®)

- 10 trials
- Dose: 1 mg to 15 mg

- Overall BPSD: Low level
- Psychosis: Mixed results
- Agitation: Most effective
Aripiprazole (Abilify®)

• 5 trials
• Dose: 2 mg to 15 mg

• Overall BPSD: Effective
• Psychosis: Low level of efficacy
• Agitation: Low level of efficacy
Quetiapine
(Seroquel®)

- 6 trials
- Dose: 25 mg to 600 mg
- Overall BPSD: low level of efficacy
- Psychosis: mixed results
- Agitation: mixed results
CATIE-AD Trial

- **Clinical Antipsychotic Trials of Intervention Effectiveness—Alzheimer’s Disease**
- 42 site, 36 week, double blind, placebo controlled trial of 421 outpatients
- Compared the effectiveness of antipsychotic medications and placebo in patients with Alzheimer’s Disease and psychosis or agitated/aggressive behavior
CATIE-AD Trial (cont.)

• Compared
  • Olanzapine, quetiapine, risperidone, to placebo

• Endpoint
  • Discontinuation
    • Any Reason
    • Lack of efficacy
    • Adverse effects, intolerability, or death
CATIE-AD Trial (cont.)

• **Results**
  • There was no differences between any agent and placebo for time to discontinuation for any reason

• **Efficacy**
  • Modest benefit
  • Favored olanzapine and risperidone
  • No significant difference in efficacy for quetiapine when compared with placebo.
CATIE-AD Trial (cont.)

- Adverse events and safety outcomes
  - Tolerability favored placebo
  - Discontinuation rates due to intolerable side effects
    - Olanzapine 24%
    - Risperidone 18%
    - Quetiapine 16%
    - Placebo 5%
CATIE-AD Trial (cont.)

- Side effects most commonly reported:
  - Parkinsonism
    - olanzapine and risperidone
  - Sedation:
    - olanzapine and quetiapine > risperidone
  - Cognitive disturbances and confusion:
    - olanzapine
    - risperidone to lesser degree
DART-AD Trial

- The Dementia Antipsychotic Withdrawal Trial
  - Assess whether continued treatment with antipsychotics in people with AD is associated with an increased risk of mortality

- Primary outcome
  - Mortality at 12 months
DART-AD Trial (cont.)

• Method
  • Between October, 2001, and December 2004, patients with AD who resided in LTC facilities in the UK were enrolled into a randomized, placebo-controlled, two-group treatment discontinuation trial. Participants were randomly assigned to continue with their antipsychotic treatment (thioridazine, chlorpromazine, haloperidol, trifluoperazine, or risperidone) for 12 months or to switch to an oral placebo.
DART-AD Trial (cont.)

• Results
  • There was a reduction in survival in the patients who continued to receive antipsychotics compared with those who received placebo.
Side Effects and Risks

Black Box Warning

Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia related psychosis treated with atypical antipsychotics are at an increased risk of death compared to placebo
Side Effects and Risks

- Extrapyramidal Side effects
  - Akathisia
  - Parkinsonism
  - Tardive Dyskinesia
  - Highest risk with risperidone; lowest with quetiapine, clozapine

- Falls
- Metabolic changes
- Orthostatic hypotension
- Sedation
- Confusion
- Tremors
Antidepressants
Antidepressants for BPSD

• Antidepressants studied
  • Sertraline
  • Citalopram
  • Fluoxetine
  • Paroxetine
  • Trazodone
Antidepressants

- 19 trials
  - 15 involved SSRI
    - 9 compared SSRI to placebo
    - 2 compared SSRI to haloperidol
    - 2 compared SSRI to risperidone
    - 1 compared SSRI to trazodone
    - 1 compared to piracetam
  - 4 involved trazodone
    - 3 compared trazodone to haloperidol
    - 1 compared trazodone to placebo
Sertraline

- Most common SSRI studied
  - 6 trials
    - 5 trials compared sertraline to placebo
    - 1 trial compared sertraline to haloperidol
  - 3 studies showed benefit
  - Well tolerated in 5 of the 6 trials
Citalopram

• 5 trials
  • 3 trials compared citalopram to placebo
  • 2 trials compared citalopram to risperidone

• 4 out of 5 trials showed benefit
• 4 out of 4 trials showed it was well tolerated
Paroxetine and Fluoxetine

- Paroxetine
  - 2 Trials
    - Mixed results

- Fluoxetine
  - 1 trial
    - No benefit
Trazodone

- 3 Trials
  - 2 trials compared trazodone to haloperidol
    - Showed benefit but benefit was comparable to haloperidol
    - Better tolerability
  - 1 trial compared trazodone to placebo
    - Showed mild benefit
    - Mild side effect profile
Citalopram: CitAD

- “Citalopram for agitation in Alzheimer’s Disease Study”
- Completed at eight academic centers in U.S. and Canada from 2009-2013
- 9 weeks
- Dosing of planned titration:
  - 10mg/day titrated to 30mg/day over 3 week period based on tolerability and response
- Results:
  - Significant difference found in favor of citalopram in agitation and caregiver distress
  - Significant difference in citalopram group for cognitive and cardiac adverse effects
- Other common reported side effects: anorexia, diarrhea and fever
- Study of subset of 48 patients that underwent enhanced monitoring after new FDA warning for risk of QTc prolongation found significant change for citalopram group as early as week 3
Side Effects and Risks

- SSRI s
  - GI effects
  - Headache
  - Dizziness
  - Possible increased risk for fractures and falls
  - Weight loss
  - SIADH
  - Tremors
  - Increased risk for bleeding
  - Risk of bone loss
  - Cardiac risk
Side Effects and Risks

- Trazodone
  - Orthostasis/Dizziness
  - Drowsiness
  - Urine retention
  - Constipation
  - Priapism
  - Agitation
Benzodiazepines
Benzodiazepines

- **Systematic Review**
  - 5 randomized clinical trials
    - Diazepam to thioridazine
    - Oxazepam to haloperidol and diphenhydramine
    - Alprazolam to lorazepam
    - Lorazepam to haloperidol
    - IM lorazepam to IM olanzapine and placebo
Benzodiazepines

• Results
  • No significant difference found in efficacy between groups, except for thioridazine being superior to diazepam
  • Two studies showed significantly higher rates of ADRs with lorazepam and haloperidol
Side Effects and Risks

Benzodiazepines

- Sedation
- Cognitive dulling
- Dizziness
- Risk for withdrawal
- Confusion
- Risk for falls
Anticonvulsants
Gabapentin

- At least 12 studies evaluated effectiveness in multiple BPSD symptoms, including agitation and aggression
  - Doses found to be effective: 300-3600mg/day
- Three studies with several case reports on the effectiveness of gabapentin in sexual inappropriateness
  - Doses found to effective: 900-2700mg/day
- Commonly reported side effects:
  - Sedation, dizziness, hallucinations, gait instability
- Dosing adjustments for renal insufficiency
Valproic Acid

- Five randomized, double-blind placebo controlled trials of valproic acid evaluating
- Only 2 studies showed improvement in agitation, but still had mixed results on other tools used to assess agitation/aggression and global symptoms
- Three other studies failed to show statistical significance over placebo for agitation, aggression, hostility or global symptoms
- Common side effects reported: sedation, GI upset, UTI, thrombocytopenia
- Conclusions: higher quality studies did not support the use of valproic acid for BPSD
Carbamazepine

- Three double-blind, placebo controlled trials
- Average dose ranges: 300-600mg/day
- One study demonstrated significant improvement in global BPSD
- All studies demonstrated significant improvements in either hostility, aggression or agitation
- Common reported side effects: sedation, dizziness and diarrhea
Side Effects and Risks

**Gabapentin**
- Sedation
- Fatigue
- Cognitive dulling
- Hallucinations
- Dizziness
- Unstable gait
- Dosing adjusted for renal impairment

**Valproic Acid**
- Elevated LFTs
- Hepatic failure
- Pancreatitis
- Sedation
- Weight gain
- Thrombocytopenia (dose dependent)
- Hyperammonemia
- Requires level monitoring
- UTI
Side Effects and Risks

Carbamazepine

- Sedation
- Dizziness
- GI upset
- Rash
- SIADH
- Elevated LFTs
- Agranulocytosis, aplastic anemia
- Level monitoring
- Significant drug interactions
Cholinesterase inhibitors (CI) and Memantine
CIs – Systematic Review

- Systematic review of the effectiveness of CIs for the management of BPSD in AD
- Included randomized, placebo-controlled trials with rivastigmine, donepezil and galantamine
- 14 studies were included
  - 9 donepezil studies
  - 3 galantamine studies
  - 2 rivastigmine studies
CIs – Systematic Review (cont)

• Results
  • 4 out of 14 studies demonstrated statistical significance in improvement in NPI scores
    • 2 donepezil studies showed overall improvement in NPI scores and 1 study showed only improvement on agitation/aggression item
    • 1 galantamine study showed overall improvement in NPI scores
  • All studies had high rates of concomitant psychotropic drug use
Memantine

• Study presenting pool data from six randomized, placebo-controlled, double-blind studies
• Behavioral symptoms assessed using total NPI scores and single-item scores
• Results:
  • Total NPI scores: memantine group showed statistically better NPI scores compared to placebo.
  • Single-item NPI scores: memantine group showed statistically better scores compared to placebo for delusions, hallucinations and agitation/aggression.
## Side Effects and Risks

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<thead>
<tr>
<th>Cholinesterase Inhibitors (CI)</th>
<th>Memantine</th>
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<tbody>
<tr>
<td>GI effects</td>
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<tr>
<td>Sleep disturbances/nightmares</td>
<td>Headache</td>
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<tr>
<td>Weight loss</td>
<td>Swelling in hands/feet</td>
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<tr>
<td>Syncope</td>
<td>Easy bruising/bleeding</td>
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<tr>
<td>Bradycardia</td>
<td>Fast heart rate</td>
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<td></td>
<td>Anxiety</td>
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<td></td>
<td>Rash</td>
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<td></td>
<td>Agitation</td>
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Miscellaneous Agents
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Propranolol

• 1 RCT
  • Propranolol was added to patient’s existing regimen and was compared to placebo
  • Average dose 106 mg +/- 38 mg/day
  • Improvement was significant for agitation/aggression and anxiety on NPI
• Side effects and risks
  • Hypotension, bradycardia
Miscellaneous Agents

Prazosin

- Up-regulation of post-synaptic alpha-1 receptors is associated with aggressive behavior in post-mortem AD studies
- 1 RCT with 22 patients
  - Compared to placebo, prazosin showed a reduction in agitation and aggression
- Side effects and Risks
  - Orthostatic hypotension, dizziness, headache, reflex tachycardia
Miscellaneous Agents
Dextromethorphan + Quinidine (Nuedexta®)

- 20mg/10mg
- Indicated for pseudobulbar affect (PBA)
- 2015 RCT compared DMX/Quinidine to placebo for AD related agitation
  - Results:
    - Reduced NPI scores in the agitation/aggression domain
    - Clinically relevant efficacy for agitation
- Side Effects and Risks
  - QT prolongation, diarrhea, dizziness, falls
  - CYP 2D6 drug interactions
Behavioral and psychological symptoms are very common in patients with AD.

Thorough assessment is needed to rule out medical or drug related causes.

Non-pharmacologic interventions should be attempted first.

Best evidence supports antipsychotics in particular risperidone, olanzapine, and aripiprazole but risks of adverse effect limit use.

Careful risk-benefit assessment and judicious prescribing may reduce the risk of serious adverse events.
References


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