Antipsychotic use in Dementia-associated Behavioral Disorders

Michael Biglow, Pharm.D, BCPS, BCPP
Clinical Pharmacy Specialist – Psychiatry
Kingsbrook Jewish Medical Center
Brooklyn, NY

Objectives

• Outline the various pathologies and presentations of dementia
• Describe the incidence and management of behavioral disorders in a demented population
• Review current literature evaluating the pharmacologic management of dementia-related behavioral disorders
• Explore recent regulatory and legal complications of antipsychotic use in demented patients
• Analyze appropriate situations in which antipsychotics would be indicated in the demented population
• Describe elements of informed consent and healthcare proxy

Background

• Types of Dementia
  • Alzheimer’s
  • Vascular
    • Multi-infarct
    • Stroke
  • Frontotemporal
  • Lewy Body
  • Parkinson’s
  • HIV/AIDS
Epidemiology

- Alzheimer’s disease is the 6th leading cause of death among American adults, and the 5th leading cause of death for adults aged 65 years and older. Notably, mortality rates for Alzheimer’s disease are on the rise, unlike heart disease and cancer death rates which are continuing to decline.
- An estimated 5.4 million Americans have Alzheimer’s disease. This number has doubled since 1980, and is expected to be as high as 16 million by 2050.
- In 2011, total Medicare and Medicaid spending for individuals with Alzheimer’s disease is estimated at $130 billion.

Alzheimer’s Criteria

- A. Development of multiple cognitive deficits
  - 1. Memory impairment
  - 2. One (or more) cognitive disturbances
    - a. Aphasia
    - b. Apraxia
    - c. Agnosia
    - d. Disturbance in executive functioning
- B. The deficits in Criteria A cause significant impairment
- C. The course of onset is gradual with a continuing cognitive decline
- D. The cognitive deficits are not due to any medical, neurologic, or substance
- E. The deficits do not occur exclusively during a course of delirium
- F. The disturbance is not better accounted for by another Axis I disorder

Alzheimer’s Criteria ...cont’d

- Additional Coding
  - Without behavioral disturbance
  - With behavioral disturbance
- Subtype
  - Early onset – onset at 65 years of age or below
  - Late onset – after age 65
Standard Pharmacologic Treatment
- Cholinesterase Inhibitors
  - Donepezil
  - Rivastigmine
  - Galantamine
  - Tacrine
- NMDA inhibitor
  - Memantine

Neuropsychiatric Complications with Dementia
- Agitation
- Aggression
- Delusions
- Hallucinations
- Repetitive vocalizations
- Wandering

Pathophysiology
- Genetics
  - Presenilin 1 correlated with psychosis
  - Polymorphisms
    - 5-HT2A 102-T/C – visual and auditory hallucinations
    - Serotonin transporter gene L/L genotype implicated with aggressive behavior
- Neurofibrillary tangles (NFTs)
  - Location
  - Density
Consequences of Neuropsych Complications

- Earlier Institutionalization
- Increased stress and burden on caregiver
- Need to exclude any medical explanations
  - Sensory impairment (hearing aid, glasses, etc.)
  - Infection
  - Dehydration
  - Pain
  - Constipation
  - Pressure sore
- Non-pharmacologic interventions should then be implemented before medications are prescribed

Nonpharmacologic interventions

- Standard Therapies
  - Behavioral
  - Reality
  - Validation
  - Reminiscence
- Alternative Therapies
  - Sensory enhancement/Relaxation methods
  - Social Contact
  - Structured Activities
  - Environmental Design
- Staff Training
  - Calming Aggressive Reactions in the Elderly (CARE)
  - Nursing Assistant Communication Skill Program

Pharmacologic Options

- No medications are FDA-approved for dementia-related behavioral disturbances
- Off-label utilization of various psychotropics
  - Antipsychotics
    - Typical
    - Atypical
  - Benzodiazepines
  - Antidepressants
  - Mood stabilizers / Anticonvulsants
  - Cholinesterase Inhibitors
  - Memantine

Cohen-Mansfield JC. Am J Ger Psych, 2001;9:361-381
Sink et al, JAMA. 2005;596-608
APA Guidelines

- Practice Guideline for the treatment of Alzheimer’s Disease and Other Dementias
- Published: October 2007
- Focus on psychiatric management and somatic treatments
- Coding
  - [I] – recommended with substantial clinical confidence
  - [II] – recommended with moderate clinical confidence
  - [III] – may be recommended on basis of individual circumstances


Psychiatric Management

- Treatment of Psychosis and Agitation
  - Class [I] recommendations
    - Assess patient safety
    - Check for underlying medical, psychiatric, or psychosocial problems
    - Antipsychotics should be used at the lowest effective dose
    - Advise patients and family of risk vs. benefit of use of drugs
  - Class [II] recommendations
    - Antipsychotics are recommended for the treatment of psychosis and/or agitation in patients with dementia
    - Limited research on use of medications past 12 weeks

Psychiatric Management ... cont’d

- Class [III] Recommendations
  - Benzodiazepines have a role in treatment of patients with prominent anxiety or on an as-needed basis for infrequent agitation or sedation
  - Lorazepam and oxazepam are preferred over long half-life benzodiazepines such as diazepam or clonazepam
  - Anticonvulsants, lithium, and beta-blockers may be considered only in patients who have failed other therapies
  - Trazodone and selective serotonin reuptake inhibitors may be appropriate in nonpsychotic patients with agitation
Antipsychotics

- First generation antipsychotics
  - “Typicals”
    - Focused on dopamine antagonism
    - Chlorpromazine first antipsychotic
    - Drug development
    - Increased potency at Dopamine type-2 (D-2) receptor
    - High potency typical antipsychotics considered metabolic neutral

Background

- Second generation antipsychotics (SGA)
  - “Atypicals”
    - Combined D-2 and serotonin (5-HT) antagonism
    - Less extrapyramidal symptoms (EPS)
    - Focus on ratio of 5-HT/D-2 blockade
    - First SGA
      - Clozapine
      - Increased metabolic side effects
      - Weight gain
      - Elevated athrogenic lipids
      - Glucose intolerance

Second Generation Antipsychotics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Weight Gain</th>
<th>Lipid Elevation</th>
<th>Risk for Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine</td>
<td>+++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>++</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Risperidone</td>
<td>++</td>
<td>D</td>
<td>D</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>++</td>
<td>D</td>
<td>D</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>++</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>+/-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Paliperidone*</td>
<td>++</td>
<td>D</td>
<td>D</td>
</tr>
<tr>
<td>Lurasidone**</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>Asenapine**</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
</tr>
</tbody>
</table>

* = increased effect, - = no effect, D = discrepant results
* Likely similar to parent compound risperidone
**Initial data limited, long-term studies needed
### Important Regulatory Events

- **1987:** Omnibus Budget Reconciliation Act (OBRA)
  - Established dosage and documentation guidelines for antipsychotic use in nursing homes
  - Appropriate supporting diagnosis
  - Target behaviors and how they change over time
  - Dosage limits
  - Side effect monitoring
  - Endorsement of alternative treatments/therapies
- **1990s:** Introduction of atypical antipsychotics with increased utilization in older population due to perceived safety benefits
- **2003:** FDA mandates label revisions for all atypicals noting increased risk of diabetes, stroke, and death
- **2005:** FDA issues black box warning

---

### Important Regulatory Events

- **April 2005:** FDA issues black box warning for all atypical antipsychotics
  - Increased risk of death 60-70% greater
  - Most deaths cardiovascular or infectious
- **2007:** Congressional testimony by FDA researcher David Graham
  - 15,000 deaths per year from off-label antipsychotic use
- **2007:** OBRA expanded to require gradual dose reduction (GDR) for NH patients on APs.
- **2008:** FDA widens black box labeling revision to conventional antipsychotics

---

### Black Box Warning

**WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS**

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo-controlled trials (median duration of 10 weeks), largely in patients taking typical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotics, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. RISPERIDAL® CONsta® (risperidone) is not approved for the treatment of patients with dementia-related psychosis. [See Warnings and Precautions (5.1)]
Studies on Efficacy

<table>
<thead>
<tr>
<th>Author</th>
<th>Drug Studied</th>
<th>Population</th>
<th>Duration</th>
<th>Primary Outcome Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Katz, 1999</td>
<td>Risperidone</td>
<td>AD, VaD, mixed; N=625</td>
<td>12</td>
<td>BEHAVE-AD</td>
</tr>
<tr>
<td>De Deyn, 1999</td>
<td>Risperidone, Haloperidol</td>
<td>AD, VaD, mixed; N=344</td>
<td>13</td>
<td>BEHAVE-AD, CMAI, CGI</td>
</tr>
<tr>
<td>Brodaty, 2003</td>
<td>Risperidone</td>
<td>AD, VaD, mixed; N=309</td>
<td>12</td>
<td>BEHAVE-AD, CMAI, CGI</td>
</tr>
<tr>
<td>Street, 2000</td>
<td>Olanzapine</td>
<td>AD; N=206</td>
<td>6</td>
<td>NPI-NH</td>
</tr>
<tr>
<td>De Deyn, 2004</td>
<td>Olanzapine</td>
<td>AD; N=652</td>
<td>10</td>
<td>NPI-NH</td>
</tr>
<tr>
<td>Zhong, 2007</td>
<td>Quetiapine</td>
<td>AD; N=333</td>
<td>10</td>
<td>PANSS-EC, CGI, NPI-NH, CMAI</td>
</tr>
</tbody>
</table>

Efficacy of pharmacologic interventions

- Sink et al. Treatment of Neuropsychiatric Symptoms of Dementia. JAMA;2005
  - Typical APs – 2/4 (Meta-analyses & RCTs) showed significant improvement but questionable clinical significance
  - Atypical Aps – 4/6 showed significant improvement, particularly risperidone and olanzapine with probable clinical significance
- Schneider et al. Effectiveness of Atypical Antipsychotic Drugs in patients with AD. NEJM;2006
  - No significant improvement in Clinical Global Impression of Change after 12 weeks, although trend of improvement seen in non-placebo groups
  - Majority of active treatment groups discontinued treatment due to adverse effects/intolerability

Impact on cognition

- Ballard et al. Quetiapine and rivastigmine and cognitive decline in Alzheimer’s disease. BMJ 2005
  - Neither rivastigmine or quetiapine improved agitation at 6 weeks
  - Quetiapine worsened cognition significantly vs. rivastigmine and placebo
- Vigen et al. Cognitive effects of atypical antipsychotic medications in patients with Alzheimer’s Disease (CATIE-AD)
  - No significant improvement in BPRS for olanzapine, risperidone, or quetiapine compared to placebo
  - Active treatment groups showed significant decline in cognitive summary score but not in any one individual cognitive assessment scale (MMSE, ADAS-cog)
**Treatment algorithm**

- **Pt with dementia + behavioral disturbance**
  - Evaluate for Delirium, Pain, or other explanations for behavior
  - Begin nonpharmacologic management
  - Educate caregivers
  - Evaluate behavior problem
- **Behavior problem improved?**
  - **Yes**: Monitor for recurrence, no begin pharmacotherapy
  - **No**: Begin pharmacotherapy

Adapted from: Sink et al. Pharmacological treatment of neuropsychiatric symptoms of dementia. JAMA 2005

---

**Treatment algorithm**

- **Depression or anxiety?**
  - **Yes**: Start trial of SSRI
  - **No**: Start trial of AChEI w/ or w/o Memantine

Behavior improved?

- **Yes**: Begin trial of antipsychotic Medication
  - Monitor for recurrence and ADRs
  - **Behavior improved?**
    - **Yes**: Consider trial of SSRi or Mood stabilizer
    - **No**: Monitor for recurrence and ADRs

---

**Mortality Risk of APs**

- Increased risk of heart disease, stroke, and chronic lower respiratory disease
- 2002, FDA report on deaths in 1452 demented patients
  - 164.7 deaths per 1000 patient years for placebo
  - 242.5 deaths per 1000 patient years for atypicals
  - 276.3 deaths per 1000 patient years for conventional APs

Mortality Risks of APs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td>1.73</td>
<td>0.7-4.3</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>1.91</td>
<td>0.79-4.59</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>1.67</td>
<td>0.7-4.03</td>
</tr>
<tr>
<td>Risperidone</td>
<td>1.3</td>
<td>0.76-2.23</td>
</tr>
<tr>
<td>Grouped</td>
<td>1.54</td>
<td>1.06-2.23</td>
</tr>
</tbody>
</table>

Schneider et al. JAMA, 2005;294:1934-1943

Comparative mortality risk of APs

<table>
<thead>
<tr>
<th>Drug</th>
<th># of patients</th>
<th>Deaths</th>
<th>Relative risk</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typical</td>
<td>353</td>
<td>49 (25.2%)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Atypical</td>
<td>9999</td>
<td>904 (22.6%)</td>
<td>0.93</td>
<td>0.75-1.16</td>
</tr>
<tr>
<td>Other psychotropics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSRIs</td>
<td>2972</td>
<td>379 (12.8%)</td>
<td>0.49</td>
<td>0.39-0.62</td>
</tr>
<tr>
<td>Other newer AD</td>
<td>843</td>
<td>133 (15.8%)</td>
<td>0.6</td>
<td>0.46-0.79</td>
</tr>
<tr>
<td>TCA</td>
<td>215</td>
<td>24 (10.2%)</td>
<td>0.4</td>
<td>0.25-0.62</td>
</tr>
<tr>
<td>Anticonvulsant</td>
<td>130</td>
<td>25 (19.2%)</td>
<td>0.79</td>
<td>0.51-1.24</td>
</tr>
<tr>
<td>Anxiolytic/Hypnotic</td>
<td>348</td>
<td>185 (19.9%)</td>
<td>0.76</td>
<td>0.59-0.98</td>
</tr>
<tr>
<td>No medication</td>
<td>12821</td>
<td>2276 (17.8%)</td>
<td>0.66</td>
<td>0.53-0.82</td>
</tr>
</tbody>
</table>


Risk of mortality among individual antipsychotics in patients with dementia

Study Design

- Retrospective chart review
- Utilized VA health system database
- Included patients >65 yo, with dementia diagnosis without exposure to antipsychotic or anticonvulsant in past 12 months
- Primary analysis:
  - Mortality within 180 days of medication initiation

Results

<table>
<thead>
<tr>
<th>Drug</th>
<th>N</th>
<th>Deaths within 180 days</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haloperidol</td>
<td>2,855</td>
<td>570</td>
<td>1.54</td>
<td>1.38-1.73</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>4,716</td>
<td>596</td>
<td>0.99</td>
<td>0.89-1.10</td>
<td>NS</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>10,651</td>
<td>933</td>
<td>0.73</td>
<td>0.67-0.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Risperidone</td>
<td>13,356</td>
<td>1,669</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Valproic Acid Derivatives</td>
<td>2,026</td>
<td>199</td>
<td>0.91</td>
<td>0.78-1.06</td>
<td>NS</td>
</tr>
</tbody>
</table>

Conclusions

- There may be differences in mortality risks among individual antipsychotics used for treating patients with dementia
- Haloperidol may carry the greatest risk among the studied medications (HR: 1.54, p<0.0001), particularly within the first 30 days
- Quetiapine has a lower risk of mortality compared to risperidone (HR: 0.73, p<0.0001)
- Valproic acid and its derivatives carry a similar mortality risk to antipsychotics
What is Informed Consent?

• Lawyer’s perspective
  • Covers MD from a possible charge of battery
  • Battery: an intentional tort representing an unwanted touching of the body
    • Treatment without informed consent
    • Patient incapable of giving consent
    • Treatment goes beyond limits of consent
    • Provider is different from one authorized
  • Can be brought even if care is well-intentioned, non-negligent, and does not cause damage

• Physician’s Perspective
  • Ethical principle of respecting patient’s autonomy
  • Method of facilitating communication

---

What is Informed Consent?

• Needed disclosures for Informed Consent
  • Diagnosis
  • Proposed treatment
  • Risks of proposed treatment
  • Reasonable alternatives
  • Prognosis of not complying with treatment

• Does not have to be a standardized form
• May indicate disclosures in progress notes

---

Issues with Informed Consent in Demented Population

• Questionable capacity to consent
  • Competence: determined by legal system
  • Capacity: determined by physician
  • Risk of coercion
Patient Case

- SC is a 83 yo WF diagnosed with Alzheimer’s 5 years ago brought in from NH complaining of wandering, increased agitation and assaulting NH staff.
- PMH: Hypothyroidism, HTN
- MMSE: 13/27 (previous score 21 3 months ago)
- Vital signs: BP - 115/76 mmHg, HR - 105 bpm
- Meds: Levothyroxine 125 mcg po qAM, Amlodipine 5 mg po qAM, Donepezil 5 mg po qhs
- Labs:

<table>
<thead>
<tr>
<th>WBC</th>
<th>Hgb</th>
<th>PLT</th>
<th>BUN</th>
<th>Cr</th>
<th>Ca</th>
<th>PT</th>
<th>TT</th>
<th>TSH</th>
</tr>
</thead>
<tbody>
<tr>
<td>138</td>
<td>110</td>
<td>41</td>
<td>98</td>
<td>10.4</td>
<td>30</td>
<td>7.5</td>
<td>184</td>
<td>2.01</td>
</tr>
</tbody>
</table>

UA: suggestive of UTI

Patient Case

- Mental Status exam:
  - Orientation: AAOx1
  - Appearance: poor eye contact, isolative, disheveled, wearing pajamas, refusing to bathe
  - Mood/Affect: irritable, labile
  - Thought process: loose associations
  - Thought content: paranoid delusions, auditory hallucinations
  - Insight/Judgment: poor

Currently excluding self to room and compliant with medications.

Time to initiate antipsychotic? NO

Progression of Care

- Initiated Cipro 500 mg po qAM for UTI
- Encouraged PO hydration
- Implemented Non-pharmacologic interventions
- On f/u 4 days later, pt continues to be reclusive, irritable
- Nursing reports pt responding to internal stimuli
- Recently attacked staff member during evening med pass
- Repeat Labs:

<table>
<thead>
<tr>
<th>WBC</th>
<th>Hgb</th>
<th>PLT</th>
<th>BUN</th>
<th>Cr</th>
<th>Ca</th>
<th>PT</th>
<th>TT</th>
<th>UA</th>
</tr>
</thead>
<tbody>
<tr>
<td>133</td>
<td>109</td>
<td>15</td>
<td>218</td>
<td>14</td>
<td>273</td>
<td>51</td>
<td>WNL</td>
<td></td>
</tr>
</tbody>
</table>

UA: WNL
What is the next step?

- Continue current medication and continue to monitor
- Continue nonpharmacologic interventions
- Increase donepezil to 10 mg po qhs
- Add memantine 5 mg po bid
- Get baseline EKG and metabolic labs, start Risperidone 0.25 mg po bid

The Bottom Line

- Antipsychotics, as a class, do increase the risk of mortality in demented patients
- Every measure to relieve behavior complications should be taken before considering pharmacologic intervention
- Maximize cognitive enhancers and/or treat underlying depression or anxiety before starting antipsychotics
- Consider avoiding the use of haloperidol as well as other antipsychotics that have a large anticholinergic burden
- Document informed consent thoroughly or consider a printed form

Questions?