Antipsychotic Use in Older Adults

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Disclosure

- I, Cherry Jackson, have no actual or potential conflict of interest in relation to this program.
Objectives

• Determine in which situations an antipsychotic would be an appropriate treatment for an older adult
• Outline first line treatments for schizophrenia, bipolar disorder, depression, and dementia
• Recognize adverse effects secondary to antipsychotics that are specific to older adults
Pre-Assessment Questions

• Which of the following is an appropriate situation to use an antipsychotic in an older adult?
  • A. Mild depression
  • B. Mixed mania
  • C. Schizophrenia
  • D. Mild dementia
Pre-Assessment Question’s

• Which of the following is a correct disease state and first line treatment?
• A. Schizophrenia: Antipsychotic
• B. Bipolar disorder: Antipsychotic
• C. Depression: Antipsychotic
• D. Dementia: Antipsychotic
Pre-Assessment Question’s

• Which of the following adverse effects is due to antipsychotics specific to older adults?
  • A. Nausea
  • B. Vomiting
  • C. Anorexia
  • D. Falls
Antipsychotic Use in Older Adults

• The population over age 60 will grow 3.5 times more rapidly than the general population.
• There is an increased urgency to examine the benefits and risks of antipsychotics in older adults.
• Antipsychotic use has been found to increase in older adults.

United Nations. Department of Economic and Social Affairs. 2001
Antipsychotic use in Older Adults

United Nations. Department of Economic and Social Affairs. 2001 

Antipsychotic Use in Older Adults

• Older patients are more likely to receive prescriptions from non-psychiatrists than from psychiatrists.
• Among patients receiving an antipsychotic, the proportion of those receiving it for >120 days was
  – 54% in individuals age 70-74
  – 49% in individuals age 75-59
  – 46% for individuals ages 80-84

Antipsychotic Use in the Older Adult

- 88% of SGAs are associated with dementia
- 22-86% of antipsychotics are used off-label
- Antipsychotics carry a “black box” warning
- Risk of death is higher with comorbid conditions

Caron L. Curr Pharm Des. 2015; 21(23):3280-97
Weintraub D. JAMA Neurol 2016;73(5):535-41
Antipsychotics in Older Adults

- Schizophrenia
- Bipolar Disorder
- Depression
- Dementia
Schizophrenia in Older Adults

- Shorter life expectancy
- Schizophrenia in individuals age >55 will double
- Antipsychotics are a first-line treatment
Antipsychotics in Older Adults with Schizophrenia

Positive Symptoms that Decline Over Time
• Hallucinations
• Delusions
• Hyperactivity

Negative Symptoms that Worsen Over Time
• Lack of Motivation
• Social Withdrawal
• Cognitive Deterioration

Schizophrenia in Older Adults

• Olanzapine vs risperidone
• 175 older adults (age ≥60 yrs)
• Mean risperidone dose = 2 mg/day
• Mean olanzapine dose = 10 mg/day

Schizophrenia in Older Adults

• Both groups improved
• Adverse events in 70% of patients
• The most common adverse effects:
  – somnolence, insomnia, dizziness, agitation, constipation, headache, and diarrhea
• Weight gain: olanzapine > risperidone

Schizophrenia in Older Adults

- Paliperidone extended-release vs placebo
- 114 older adults (age >65 years)
- No statistically significant difference in efficacy between placebo vs paliperidone
- Adverse reactions included increased prolactin with paliperidone

Schizophrenia in Older Adults

- Clozapine 300 mg/day vs chlorpromazine 600 mg/day
- 42 older adults (mean age 67 years)
- Adverse effects:
  - Drooling, hematologic abnormalities, sedation, tachycardia, EPS, and weight gain

Antipsychotic Adverse Effects

• A >40% reduction in antipsychotic dose was associated with reduced adverse effects, particularly extrapyramidal side effects and elevations of prolactin levels.

Graff-Guerrero A. JAMA Psychiatry.2015;72(9):927-34.
Bipolar Disorder in Older Patients

- Up to 25% of individuals with bipolar disorder are elderly and that number is predicted to increase over the next decade.

Sajatovic M. Psychiatr Serv 2004;559(9):1014-21.
Jeste DV. Arch Gen Psychiatry 1999;56(9):848-53.
## Antipsychotics in Older Adults with Bipolar Disorder

<table>
<thead>
<tr>
<th>Considerations in Older Adults with Bipolar Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bipolar manic episodes may be reduced or attenuated</td>
</tr>
<tr>
<td>Bipolar depressive symptoms may be more prominent and exert longer-term impact on functioning</td>
</tr>
<tr>
<td>Cognitive deterioration may occur over time</td>
</tr>
<tr>
<td>Medical comorbidity is extensive with 3 to 6 chronic medical conditions being the norm</td>
</tr>
</tbody>
</table>

Bipolar Disord 2015;17(7):689-704
Bipolar Disorder in Older Patients

- Lithium, mood stabilizers - first line treatment
- SGAs are approved for bipolar mania.
- The olanzapine-fluoxetine combination, quetiapine and lurasidone are approved for bipolar depression.
- Aripiprazole, olanzapine, quetiapine, ziprasidone, and long acting injectable risperidone are FDA approved for longer term use in adults with bipolar disorder.
- No head to head trials of antipsychotics in older persons

Pillarella J. Psychiatr Serv 2012;63(1):83-86
De Fruyt J. J Psychopharmacol. 2012; 26(5):603-17
Antipsychotics in Bipolar Depression

- DBPC trial in bipolar depression
- Quetiapine vs placebo
- Response in patients older than 65 years old was better with quetiapine 600 mg/day

Bipolar Depression in Older Patients

• Lurasidone for bipolar depression
• Monotherapy (83 patients) 20-60 mg or 80-120mg vs. placebo
• Adjunct lurasidone (53 patients) 20-120 mg/day or placebo with lithium or valproate
• Lurasidone > placebo
• Adjunct lurasidone showed no significant improvement over lithium or valproate

Sajatovic M. Paper presented at: ACNP 53rd Annual Meeting 2014; Phoenix
Antipsychotics in Older Adults

• In older patients with bipolar disorder, consider the role of antipsychotics in relation to the use of lithium and mood stabilizers

Bipolar Depression in Older Patients

- Lurasidone side effects: nausea, somnolence
- Akathisia and insomnia were ADRs at doses > 80 mg/day
- Weight changes were no greater than placebo

Sajatovic M. Paper presented at ACNP 53rd Annual Meeting; 2014, Phoenix
Bipolar Depression in Older Adults

- Open study of aripiprazole (10.3 mg/day)
  - ADR’s: restlessness, weight gain, sedation
- Open study of asenapine (11.2 mg/day)
  - ADR’s: GI distress, restlessness, tremor, decreased cognition, sluggishness

Bipolar Mania in Older Adults

• Quetiapine vs placebo in mania
• Mania improved with 550 mg vs placebo
• ADRs: dry mouth, somnolence, orthostasis, insomnia, weight gain, dizziness

Bipolar Mania in Older Adults

- Case series of 11 patients receiving asenapine for mania
- 63% remission rate.
- ADR’s: rash, edema, sedation

Bipolar Mania in Older Adults

• 94 patients with mania received olanzapine, VPA or placebo
• Patients receiving olanzapine and VPA improved; placebo did not
• Safety was the same for older vs younger patients.

### Summary

#### Patients with Schizophrenia or Bipolar

- The number of older adults with mental illness is increasing
- Antipsychotics are extensively used in older patients
- Randomized controlled trials or prospective naturalistic studies
- The evidence base is fairly solid on several key points:
  - Second-generation antipsychotics are preferred
  - SGAs are relatively safe and well-tolerated for older patients
  - Older adults are more likely to experience adverse effects

- Additional research is needed to provide detailed and conclusive information regarding relative risks and burdens of using antipsychotics in geriatric patients.

Gildengers AG. Bipolar Disorder 2014; 16(6):617-23.
Depression in Older Adults

• The prevalence of MDD symptoms in older adults is 3 to 4%
• Clinically significant depressive symptoms in community dwelling older adults has ranged up to 15%
• The prevalence of depression in nursing homes is as high as 50%

Depression in Older Adults

• Late-life depression needs to be recognized and treated aggressively.

• Antidepressants are the mainstay of pharmacotherapy
  – First line – SSRI’s (escitalopram or sertraline)
  – Second line – SNRI’s (duloxetine or venlafaxine)
  – Third line- bupropion or nortriptyline

• Antipsychotics also have a role

Mulsant BH. APA Textbook of Geriatric Psychiatry
2015;527-87.
## Depression in Older Patients

### FDA Indications for Antipsychotics in Patients with MDD

<table>
<thead>
<tr>
<th>Drug</th>
<th>Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td>Adjunctive treatment of MDD in adults</td>
</tr>
<tr>
<td>Brexpiprazole</td>
<td>Adjunctive treatment of MDD in adults</td>
</tr>
<tr>
<td>Olanzapine-fluoxetine combination</td>
<td>Acute and maintenance treatment of treatment-resistant depression in adults and geriatric adults</td>
</tr>
<tr>
<td>Quetiapine XR</td>
<td>Treatment of MDD as monotherapy in adults; adjunctive treatment of MDD in adults and geriatric adults who have had an inadequate response to antidepressants alone.</td>
</tr>
</tbody>
</table>

Depression in Older Patients

• Antipsychotics have a “black box” warning for serious adverse events in older adults with dementia
  – death due to cardiac events
  – infections

• Limit the use of antipsychotics to psychotic and treatment resistant depression

US FDA. Public Health Advisory.
https://www.fda.gov/drugs/drugsafety/postmarketdrug
safetyinformationforpatientsandproviders/ucm053171
Depression in Older Adults

- Olanzapine plus placebo vs olanzapine plus sertraline
- 259 patients with psychotic depression
- 142 patients were ≥60
- Mean sertraline dose was 165.7 mg
- Mean olanzapine dose was 13.4 mg

Depression in Older Adults

• Olanzapine plus sertraline was more efficacious than olanzapine plus placebo.

Depression in Older Adults

• DB study of venlafaxine plus aripiprazole vs venlafaxine plus placebo
• 181 patients >60 years of age
• If patients did not respond, aripiprazole was added, leading to 44% rate of remission

Lenze EJ. Lancet 2015;386(10011):2404-12
Depression in Older Patients

- No response to 1 to 3 antidepressants
- 110 patients >55 years
- Citalopram up to 30 mg/day initiated
- Non-responders received augmentation with risperidone
- Sixty-three (68%) patients remitted
- Randomized to citalopram plus risperidone vs citalopram plus placebo.
- Neither the time to relapse or relapse rate differed significantly.

Depression in Older Adults

- RCT of placebo vs quetiapine XR
- Quetiapine associated with a significantly larger reduction in depressive symptoms

## Depression in Older Adults

Clinical Date Relevant to Using Antipsychotics in Older Patients with MDD

<table>
<thead>
<tr>
<th>Clinical Indications</th>
<th>Evidence for Use of</th>
<th>Clinical Concerns</th>
</tr>
</thead>
<tbody>
<tr>
<td>Augmentation of an antidepressant in presence of psychotic features (“psychotic depression”)</td>
<td>Olanzapine, Perphenazine</td>
<td>Weight gain, falls, pedal edema, Extrapyramidal symptoms, tardive dyskinesia</td>
</tr>
<tr>
<td>Augmentation of an antidepressant for treatment-resistant depression</td>
<td>Aripiprazole, Risperidone</td>
<td>Akathisia, falls, weight gain, Falls, weight gain</td>
</tr>
<tr>
<td>Monotherapy as an alternative to an antidepressant</td>
<td>Quetiapine</td>
<td>Somnolence, dry mouth, extrapyramidal symptoms</td>
</tr>
</tbody>
</table>

## Depression in Older Adults

<table>
<thead>
<tr>
<th>Adverse effects of antipsychotics in older patients with MDD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive impairment</td>
</tr>
<tr>
<td>Metabolic changes including weight gain and metabolic syndrome</td>
</tr>
<tr>
<td>Extrapyramidal symptoms and tardive dyskinesia</td>
</tr>
<tr>
<td>Dizziness, orthostatic hypotension, falls and fractures</td>
</tr>
<tr>
<td>Prolonged QTc, Torsade de pointes, and sudden death</td>
</tr>
</tbody>
</table>

Summary

• An antidepressant and a lower dose of antipsychotic is first line therapy in patients with MDD with psychotic features or treatment-resistant depression.

• The literature does not provide much guidance using antipsychotics in older patients with MDD

Antipsychotic Use in Dementia

- 25 million patients currently have a diagnosis of dementia.
- 5.3 million were diagnosed with Alzheimer’s disease in the US in 2010 alone.
- 1/3 of all patients are mildly impaired
- 2/3 of all patients are moderately impaired

www.alzheimers_disease_facts_figures.asp
Antipsychotic Use in Dementia

• 88% of Medicare claims for SGA’s used for dementia.
• Long-term prescribing is the most common inappropriate prescribing practice
• Up to 86% of antipsychotic prescribing is off-label.

Caron L. Curr Pharm Des. 2015;21(23);3280-97.
Antipsychotic Use in Dementia

- FDA “black box” warning for antipsychotics leading to increased risk of death
- Risk of death is increased when prescribing antipsychotics for comorbid conditions

### Common Behavioral Symptoms in Dementia (BPSD)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aggression/Agitation</td>
<td>20-80%</td>
</tr>
<tr>
<td>Sleep wake disturbance</td>
<td>42%</td>
</tr>
<tr>
<td>Delusions</td>
<td>9-63%</td>
</tr>
<tr>
<td>Depression/dysphoria</td>
<td>38%</td>
</tr>
<tr>
<td>Physical aggression</td>
<td>31-42%</td>
</tr>
<tr>
<td>Disinhibition</td>
<td>36%</td>
</tr>
<tr>
<td>Apathy</td>
<td>72%</td>
</tr>
<tr>
<td>Sundowning</td>
<td>18%</td>
</tr>
<tr>
<td>Anxiety</td>
<td>48%</td>
</tr>
<tr>
<td>Hypersexuality</td>
<td>3%</td>
</tr>
<tr>
<td>Psychomotor disturbance</td>
<td>46%</td>
</tr>
<tr>
<td>Euphoria</td>
<td>2%</td>
</tr>
<tr>
<td>Irritability/lability</td>
<td>42%</td>
</tr>
<tr>
<td>Obsessive compulsive</td>
<td>2%</td>
</tr>
</tbody>
</table>

Use of Antipsychotics in Dementia

• Behavioral symptoms are common in dementia
• Non-pharmacologic measures are first-line
• SGAs have the strongest evidence for BPSD,

Sink KM. JAMA 2005;293(5):596-608
Use of Antipsychotics in Dementia

- CATIE-AD
- RCT 421 outpatients with BPDS
- Randomized to an SGA (risperidone, olanzapine, quetiapine) or placebo.
- SGAs had a higher rate of parkinsonism or EPS, sedation, confusion, changes in mental status, and increase in weight and BMI

Schneider L, et al. NEJM 2006;355:1525
Use of Antipsychotics in Dementia

- Cardiac adverse effects and pneumonia - primary causes of death
- Limited data on cardiac adverse effects
- One study found an increase in those taking FGAs compared with SGAs.

US FDA. Public Health Advisory.
https://www.fda.gov/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm053171
Use of Antipsychotics in Dementia

- 2005 -retrospective cohort study by Wang and colleagues
  - Mortality higher with FGA vs. SGA
  - Higher doses
  - First 40 days

Use of Antipsychotics in Dementia

- “Black box” warning added in 2005 for SGA’s
- “Black box” warning added in 2008 for FGA’s

Use of Antipsychotics in Dementia

• Study of mortality risk associated with antipsychotics
• 33,000 older veterans with dementia started on haloperidol, risperidone, olanzapine, quetiapine, or valproic acid
• Highest mortality was associated with haloperidol >risperidone = olanzapine > valproic acid = quetiapine.

Use of Antipsychotics in Dementia

• Retrospective case controlled study
• 90,786 patients age ≥65 with dementia
• Calculated NNH over 180 days following initiation of an FGA or SGA.
• NNH:
  – Haloperidol 26 (95% CI 15-99)
  – Risperidone 27 (95% CI 19-46)
  – Olanzapine 40 (95% CI 21-312)
  – Quetiapine 50 (95% CI 30-150)

Sultana J. Analysis 2008;179:438-46
Use of Antipsychotics in Dementia

- AP use is common in dementia
- Rate of antipsychotic use in older adults with dementia living in the community was approximately 19%
- Rate of antipsychotic use at the VA found that use was approximately 18%

Kales HC. Arch Gen Psychiatry 2011;68(2):190-7
Use of Antipsychotics in Dementia

• Use of SGAs began to decline in 2003
• Olanzapine and risperidone use declined between 2003-2005, whereas quetiapine use significantly increased
• All 3 SGAs declined after the black-box warning leveling off to approximately 12% by 2007
• 14% of Medicare Part D enrollees with dementia living in the community were prescribed an antipsychotic in 2012.

Use of Antipsychotics in Dementia

• BPSD is a common reason for nursing home placement.
• 24-32% of nursing home residents were treated with antipsychotics.
• 26% of residents in VA nursing homes were prescribed antipsychotics in 2004-2005.

Chen Y. Arch Intern Med 2010;170(1):89-95
Feng Z. Int J Geriatr Psychiatry 2009;24(10):1110-8
Gellad WF. Med Care 2012;50(11):954-60.
Use of Antipsychotics in Dementia

• CMS lowered antipsychotic use from 24% in long-stay nursing home residents nationwide in 2011 to 19% by the end of 2014.

• 40% of nursing home residents with cognitive impairment and behavioral issues and without psychosis received antipsychotics.

• 33% of Medicare Part D enrollees with dementia who spent >100 days in a nursing home were prescribed an antipsychotic in 2012.

Use of Antipsychotics in Dementia

• Three-fourths of all patients with dementia in long term care are given at least one psychotropic.
• 7 out of 10 receiving an SGA.

Vasudev A. Am J Geriatr Psychiatry. 2015;23(12):1259-69
Using Antipsychotics in Dementia

Use DICE before prescribing an antipsychotic to a person with dementia

<table>
<thead>
<tr>
<th>Use DICE before prescribing an antipsychotic to a person with dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Describe the behavioral symptoms fully (including who, what, when, and where).</td>
</tr>
<tr>
<td>Investigate the possible underlying causes of the behavior:</td>
</tr>
<tr>
<td>• Person with the dementia (e.g., pain, infection, sensory changes, ADRs)</td>
</tr>
<tr>
<td>• Caregiver (e.g. negative communication style such as yelling at the person with dementia, mismatch of expectations with level of dementia)</td>
</tr>
<tr>
<td>• Environment (e.g. overstimulation with clutter and blaring TV)</td>
</tr>
</tbody>
</table>

Using Antipsychotics in Dementia

**Use DICE before prescribing an antipsychotic to a person with dementia**

<table>
<thead>
<tr>
<th>Create a treatment plan:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Providing the caregiver with education/support</td>
</tr>
<tr>
<td>• Enhancing the caregivers communication</td>
</tr>
<tr>
<td>• Creating meaningful activities</td>
</tr>
<tr>
<td>• Simplify tasks</td>
</tr>
<tr>
<td>• Ensuring the environment is safe</td>
</tr>
<tr>
<td>• Adjusting the stimulation in the environment</td>
</tr>
</tbody>
</table>

Evaluate the impact of any interventions. First-line use of antipsychotics should be limited to psychosis or aggression that is causing harm, significantly distressing to the person, impairing function, or creating a safety risk

Using antipsychotics in older patients with dementia: a summary of the evidence

| SGAs have the strongest evidence base although benefits are moderate at best. |
| In terms of individual SGAs, the best evidence is for risperidone for aggression |
| FGAs have no clear evidence for BPSD. There may be slight benefit for haloperidol for aggression, but this medication has a higher mortality risk than SGAs |
| In terms of mortality risk, FGAs have a higher risk than SGAs, and SGAs have a higher risk than most other psychotropics |
| Individual SGAs also differ in mortality risk, with risperidone having the highest risk, followed by olanzapine, then quetiapine |
| Because of the nature of risk-benefit with both FGAs and SGAs in dementia, these agents should be reserved for cases where there is considerable risk of harm to self or others |

# Antipsychotic Adverse Effects

<table>
<thead>
<tr>
<th>Antipsychotic Adverse Effects in Older Adults</th>
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<tbody>
<tr>
<td>Cardiovascular changes</td>
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<tr>
<td>Hematologic changes</td>
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<tr>
<td>Metabolic/endocrine changes</td>
</tr>
<tr>
<td>Electrolyte imbalance</td>
</tr>
<tr>
<td>Extrapyramidal symptoms and tardive dyskinesia</td>
</tr>
<tr>
<td>Adverse effects that may be related to peripheral and central anticholinergic effects</td>
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<tr>
<td>Adverse effects that may be related to antiadrenergic effects</td>
</tr>
<tr>
<td>Adverse effects that may be related to antihistaminic effects</td>
</tr>
<tr>
<td>Drug-drug interactions due to medical comorbidity</td>
</tr>
</tbody>
</table>

Generally, medical comorbidity becomes more prominent and antipsychotics need to be co-prescribed carefully to avoid interactions with other medications for medical conditions.

*Textbook of Geriatric Psychiatry. 2015; 527-87.*
Conclusion

- Antipsychotics are often used in older patients.
- Antipsychotics are first line in schizophrenia, but not for other disorders.
- 88% of Medicare prescriptions for SGA’s are used in off-label in individuals with BPSD.
- Antipsychotics cause significant adverse events in older adults, and are worse if the individual has comorbid conditions.
- Antipsychotics increase morbidity and mortality.
Post-Assessment Questions

• Which of the following is an appropriate situation to use an antipsychotic in an older adult?
  • A. Mild depression
  • B. Mixed mania
  • C. Schizophrenia
  • D. Mild dementia
Post-Assessment Question’s

Which of the following is a correct disease state and first line treatment?

- A. Schizophrenia: Antipsychotic
- B. Bipolar disorder: Antipsychotic
- C. Depression: Antipsychotic
- D. Dementia: Antipsychotic
Post-Assessment Question’s

• Which of the following adverse effects is due to antipsychotics specific to older adults?
  • A. Nausea
  • B. Vomiting
  • C. Anorexia
  • D. Falls
Questions?