Geropsychopharmacology: Myth and Tradition vs. Evidence

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Disclosures

The speaker has no commercial interest to disclose. Off-label medication use will be discussed.
Objectives

1. Review the myths of psychopharmacology in elders
2. Examine the evidence on the neurochemical changes associated with aging
3. Examine the evidence on current traditional use of psychotropics with the elderly
4. Examine the evidence based effectiveness of psychopharmacology with aging disorders

Geropsychopharmacology

- 21,526 older adults: median age of 84
- In Community
- 1.1% on antipsychotics
- In Care Agency
- 20 times more likely to be on Antipsychotics

Rochon et al. 2013
Antipsychotic Use with Elders: US

<table>
<thead>
<tr>
<th>Medication</th>
<th>Weighted Frequency</th>
<th>Percentage</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antipsychotic use</td>
<td>227 722</td>
<td>32.88</td>
<td>31.50, 34.26</td>
</tr>
<tr>
<td>Atypical</td>
<td>219 071</td>
<td>31.63</td>
<td>30.27, 33.00</td>
</tr>
<tr>
<td>olanzapine</td>
<td>76 626</td>
<td>11.06</td>
<td>10.14, 11.99</td>
</tr>
<tr>
<td>risperidone</td>
<td>73 782</td>
<td>10.65</td>
<td>9.76, 11.55</td>
</tr>
<tr>
<td>quetiapine</td>
<td>64 213</td>
<td>9.27</td>
<td>8.41, 10.13</td>
</tr>
<tr>
<td>ziprasidone</td>
<td>4 107</td>
<td>0.59</td>
<td>0.38, 0.80</td>
</tr>
<tr>
<td>aripiprazole</td>
<td>6 162</td>
<td>0.89</td>
<td>0.62, 1.16</td>
</tr>
<tr>
<td>Typical</td>
<td>12 123</td>
<td>1.75</td>
<td>1.37, 2.13</td>
</tr>
<tr>
<td>haloperidol</td>
<td>8 064</td>
<td>1.16</td>
<td>0.86, 1.47</td>
</tr>
<tr>
<td>others</td>
<td>4 230</td>
<td>0.61</td>
<td>0.38, 0.84</td>
</tr>
</tbody>
</table>

Kamble, Chen, Sherer, & Aparasu 2009

Elders in Nursing Homes: US Rate

- 1 of 3 elderly LTC residents with dementia used antipsychotic agents, mainly atypical
- Olanzapine,
- Risperidone and
- Quetiapine highest use

Kamble, Chen, Sherer, & Aparasu 2009
• Psychiatric disorders such as anxiety were associated with use of atypical agents with dementia.
• Predisposing factors 1. male, 2 bed capacity
• Need factors 1. decision-making 2. depression 3. behavioral symptoms, 4. ADLs, and 5. bed mobility

8.2% were put on antipsychotics, 14.8% were given hypnotics and 7.8% were prescribed anxiolytic.

Six months after admission to a care home, 30.2% of all new residents had received at least one prescription for an antipsychotic, 37.1% for a hypnotic and 24.5% for an anxiolytic.
Myths: Setting the Stage for Pharmacological Misuse

- Older adults complain.
- Older adults are negative.
- Older adults have rigid personalities.
- Dementia is normal for aging.
- Any cognitive impairment is Alzheimer’s.

Myths (cont.)

- Genetics determine illness and disability;
- Disability is inevitable;
- Loss of social ties leaves elders alone and isolated;
- Most elderly are depressed, demented, or dependent;

Kennedy, 2003
Myths (cont.)

- All Elders have a chronic illness,
- Aging eliminates individual needs\potential
  - physiologic and social homogeneity
- Pharmacology is the most important factor to reduce dependency;
- The older the patient, the greater the cost.

Kennedy, 2003

Neurochemistry Myths

- Adult age- Adult Psychopharmacology
- Psychiatric meds control behaviors
- Psychiatric meds only affect the brain
- Learning capacity declines
Traditional Geropsychopharmacology

- Anxiolytics
- Antidepressants
- Antipsychotics
- Antiepileptic Medications
- Off Label Use – FDA Designation
- Traditional Wisdom is… Use one third the normal adult dose to adjust for metabolism.

### Anxiolytic use

<table>
<thead>
<tr>
<th>Generic (Brand Name)</th>
<th>Initial Dosage</th>
<th>Maximum Daily Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alprazolam (Xanax®)</td>
<td>0.125 mg to 0.25 mg BID</td>
<td>0.25 mg to 2 mg BID</td>
</tr>
<tr>
<td>Lorazepam (Ativan®)</td>
<td>0.25 mg to 0.5 mg BID</td>
<td>0.5 mg to 4 mg BID</td>
</tr>
<tr>
<td>Oxazepam (Serax®)</td>
<td>10 mg BID</td>
<td>10 mg to 30 mg BID</td>
</tr>
<tr>
<td>Temazepam (Restoril®)</td>
<td>7.5 mg Q HS</td>
<td>7.5 mg to 5 mg Q HS</td>
</tr>
<tr>
<td>Eszopiclone (Lunesta®)</td>
<td>1 mg to 2 mg Q HS</td>
<td>1 mg to 2 mg Q HS</td>
</tr>
<tr>
<td>Gabapentin (Neurontin®)</td>
<td>100 mg Q HS</td>
<td>100 mg to 300 mg /3600 mg² Q HS</td>
</tr>
<tr>
<td>Mirtazapine (Remeron®)</td>
<td>7.5 mg Q HS</td>
<td>7.5 mg to 45 mg Q HS</td>
</tr>
<tr>
<td>Nortriptyline (Pamelor®)</td>
<td>10 mg to 25 mg Q HS</td>
<td>10 mg to 100 mg Q HS</td>
</tr>
<tr>
<td>Trazodone (Desyrel®)</td>
<td>25 mg Q HS</td>
<td>25 mg to 200 mg Q HS</td>
</tr>
<tr>
<td>Zaleplon (Sonata®)</td>
<td>5 mg Q HS</td>
<td>5 mg to 10 mg Q HS</td>
</tr>
<tr>
<td>Zolpidem (Ambien®)</td>
<td>5 mg Q HS</td>
<td>5 mg to 10 mg Q HS</td>
</tr>
</tbody>
</table>

Lindsey, 2009
### Antidepressants Elders

<table>
<thead>
<tr>
<th>Generic (Brand) Name</th>
<th>Starting Dosage</th>
<th>Daily Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citalopram (Celexa®)</td>
<td>10 mg to 20 mg per day</td>
<td>10 mg to 40 mg per day</td>
</tr>
<tr>
<td>Escitalopram (Lexapro®)</td>
<td>10 mg per day</td>
<td>5 mg to 20 mg per day</td>
</tr>
<tr>
<td>Fluoxetine (Prozac®)</td>
<td>10 mg per day</td>
<td>5 mg to 40 mg per day</td>
</tr>
<tr>
<td>Paroxetine (Paxil®, Paxil CR®)</td>
<td>10 mg per day</td>
<td>5 mg to 40 mg per day</td>
</tr>
<tr>
<td>Sertraline (Zoloft®)</td>
<td>12.5 mg to 25 mg per day</td>
<td>25 mg to 200 mg per day</td>
</tr>
<tr>
<td>Bupropion (Wellbutrin®, Wellbutrin SR®, Wellbutrin XL®)</td>
<td>37.5 mg to 75 mg per day; SR: 75 mg to 100 mg every morning; XL: 150 mg every morning</td>
<td>150 mg in two to three divided dosages; SR: 100 mg twice per day; XL: 150 mg per day</td>
</tr>
<tr>
<td>Duloxetine (Cymbalta®)</td>
<td>20 mg per day</td>
<td>20 mg to 60 mg per day</td>
</tr>
<tr>
<td>Mirtazapine (Remeron®, Remeron SolTab®)</td>
<td>7.5 mg at bedtime</td>
<td>7.5 mg to 45 mg at bedtime</td>
</tr>
<tr>
<td>Venlafaxine (Effexor®, Effexor XR®)</td>
<td>25 mg twice per day; XR: 37.5 mg per day</td>
<td>150 mg per day in divided dosages; XR: 150 mg per day</td>
</tr>
<tr>
<td>Desipramine (Norpramin®)</td>
<td>25 mg per day</td>
<td>100 mg per day</td>
</tr>
<tr>
<td>Nortriptyline (Pamelor®)</td>
<td>10 mg to 25 mg per day</td>
<td>50 mg per day</td>
</tr>
</tbody>
</table>

### Antipsychotic Use

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Starting Dosage</th>
<th>Daily Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haloperidol (Haldol®)</td>
<td>0.25 mg to 0.5 mg per day</td>
<td>0.25 mg to 4 mg per day</td>
</tr>
<tr>
<td>Aripiprazole (Abilify®)</td>
<td>5 mg per day</td>
<td>2.5 mg to 15 mg per day</td>
</tr>
<tr>
<td>Olanzapine (Zyprexa®)</td>
<td>2.5 mg per day</td>
<td>2.5 mg to 15 mg per day</td>
</tr>
<tr>
<td>Quetiapine (Seroquel®)</td>
<td>25 mg at bedtime</td>
<td>50 mg to 400 mg at bedtime</td>
</tr>
<tr>
<td>Risperidone (Risperdal®)</td>
<td>0.25 mg to 0.5 mg at bedtime</td>
<td>0.25 mg to 3 mg at bedtime</td>
</tr>
<tr>
<td>Ziprasidone (Geodon®)</td>
<td>20 mg twice per day with food</td>
<td>20 mg to 80 mg twice per day with food</td>
</tr>
</tbody>
</table>
## Risks of Falls with Drug Classes

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Adjusted Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sedatives and hypnotics</td>
<td>1.47 (1.35 – 1.62)</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>1.41 (1.20 – 1.71)</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>1.36 (1.13 – 1.76)</td>
</tr>
</tbody>
</table>

Wollcott et al. 2009

## Adverse Events with Psychotropics

- 1,889 (8.8%) had a serious event
  - (1,044 women, 7.6%; 845 men, 10.9%),
- 718 (3.3%) died
  - (363 women, 2.6%; 355 men, 4.6%),
- 1,467 (6.8%) had a hospital admission
  - (812 women, 5.9%; 655 men, 8.4%) within 30 days.
- Men were 47% more likely than women to have a serious event

Rochon et al. 2013
Black BOX: FDA Warning

Warning: Increased Mortality in Elderly Patients with Dementia-Related Psychosis

See full prescribing information for complete boxed warning.

Elderly patients with dementia related psychosis treated with antipsychotic drugs are at an increased risk of death.

This medication is not approved for use in patients with dementia-related psychosis.

The Evidence!

- Anxiolytics
- Antidepressants
- Antipsychotics
- Off Label Use – FDA Designation
Aging Neurochemistry Reality

- Neurophysiologic capacity
- Physiological capacity
- Metabolic capacity

Natural Volumetric Loss

Hedden and Gabrieli 2004
Dopamine

- Age-related changes in
- Dopamine synthesis,
- Dopamine binding sites,
- Decrease in $D_1$ and $D_2$ receptors
- Significant declines in dopamine receptors, $D_2$ and $D_3$

Dopamine Receptor Modulation

![Diagram of Dopamine Signaling and Receptor Modulation](image)

*Figure 1. Schematic life span gradients of subcortical and cortical dopamine modulation. The maturation of the cortical system is more protracted than that of the subcortical system, which peaks in adolescence.*

Anyanwu 2007
Serotonin

- Decreasing levels of different serotonin receptors and
- Serotonin transporter, 5-HTT (Yamamoto et al. 2001)

Serotonin Receptor Density Decline (Tauscher et al. 2002)
**Blood Brain Barrier Aging**

- Different changes in development and aging, leading to an optimal amino acid transport
- Minimum penetration of lipophilic agents in the adult brain, reducing transport and increasing the penetration of lipophilic compounds

  Anyanwu, E. 2007

**Neurochemical Aging**

- Levels of neurotransmitters (Acetylcholine (ACh), serotonin (5-HT), and dopamine) levels are all decreased
- Metabolic enzyme activities such as choline acetyltransferase and choline esterase increase.

  Anyanwu, E. 2007
Neurotransmitters with Aging

- Metabolic enzyme activities of choline acetyltransferase and choline esterase activities increase.
- Tryptophan hydroxylase activity is not affected.
- Monoamine oxidase-A increases

Pharmacokinetics Principles in Aging

- Rate of Absorption
- Rate of Excretion
- Rate of Elimination
Liver function

• Changes in the hepatic sinusoid have been identified that contribute to the substantial age-related changes in liver function.

• Reduction in capacity to metabolize

Renal Aging

• A progressive linear decline in clearance from 140 ml/min/1.73m2 at age 30 to 97 at age 80

• 254 "normal" subjects, the mean decrease in creatinine clearance was 0.75 ml/min/year.

• Decline in renal function is associated with co-existing cardiovascular diseases and risk factors.
Respiratory Capacity and PO2 Exchange

Evidence For Geropsychopharmacology

- Based on systematic reviews
- Evidence Based Practices
Anxiolytics in use

- Buspirone
- Chlordiazepoxide
- Diazepam, 
- Lorazepam
- Hydroxyzine

Anxiolytics Evidence Based

- No controlled trials support use of benzodiazepines in the treatment of non-alcohol withdrawal related delirium and
- At this time benzodiazepines cannot be recommended for the control of agitation in dementia/delirium.

Lonergan, Luxenberg, Sastre. 2009
Depression in Dementia

- Depression affects up to 50% of persons with dementia
- Commonly treated with Antidepressants

Schwarz Froelich & Burns 2012

Typical Elder Antidepressants

- Tricyclic antidepressants
- SSRI’s
- SNRI’s
- Atypical Antipsychotics
All TCAs versus SSRIs, Outcome

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>All TCAs</th>
<th>SSRIs</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>De Ronchi 1998</td>
<td>15/33</td>
<td>16/32</td>
<td>1.0%</td>
<td>0.91</td>
<td>0.55, 1.51</td>
<td></td>
</tr>
<tr>
<td>Dorman 1991</td>
<td>23/28</td>
<td>15/29</td>
<td>1.5%</td>
<td>0.91</td>
<td>0.59, 1.35</td>
<td></td>
</tr>
<tr>
<td>Fronczek 1995</td>
<td>80/164</td>
<td>80/197</td>
<td>14.3%</td>
<td>1.01</td>
<td>0.67, 1.57</td>
<td>0.75</td>
</tr>
<tr>
<td>Gottegger 1995</td>
<td>29/17</td>
<td>22/14</td>
<td>10.4%</td>
<td>1.23</td>
<td>0.85, 1.79</td>
<td>1.04</td>
</tr>
<tr>
<td>Hutchison 1991</td>
<td>13/32</td>
<td>26/58</td>
<td>6.1%</td>
<td>0.91</td>
<td>0.55, 1.41</td>
<td>1.04</td>
</tr>
<tr>
<td>Kyle 1999</td>
<td>80/164</td>
<td>80/179</td>
<td>22.3%</td>
<td>1.60</td>
<td>1.34, 1.94</td>
<td>1.32</td>
</tr>
<tr>
<td>Malenst 1998</td>
<td>20/24</td>
<td>20/42</td>
<td>6.0%</td>
<td>1.09</td>
<td>0.56, 2.10</td>
<td>1.05</td>
</tr>
<tr>
<td>Nosse 2001</td>
<td>26/27</td>
<td>25/29</td>
<td>17.2%</td>
<td>0.88</td>
<td>0.56, 1.37</td>
<td>1.04</td>
</tr>
<tr>
<td>Pelchat 1993</td>
<td>26/42</td>
<td>26/44</td>
<td>8.5%</td>
<td>1.41</td>
<td>0.89, 2.25</td>
<td>1.39</td>
</tr>
</tbody>
</table>

Total (95% CI) 528 552 100.0% 1.67 [0.94, 2.22]

TCA vs SSRI Pooled studies

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Failed to recover</td>
<td>9</td>
<td>1080</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>1.07 [0.94, 1.22]</td>
</tr>
<tr>
<td>2 Depression severity (HAMD State)</td>
<td>2</td>
<td>90</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>2.41 [3.08, 8.50]</td>
</tr>
<tr>
<td>3 Withdrawal due to side-effects</td>
<td>12</td>
<td>1207</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>1.56 [1.09, 1.70]</td>
</tr>
<tr>
<td>4 Total withdrawal rates</td>
<td>14</td>
<td>1328</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>1.23 [1.05, 1.43]</td>
</tr>
</tbody>
</table>
• Limited data
• Dual-action agents (either TCAs or SNRIs) do not use any additional benefits in efficacy over SSRI’S for the elderly.

Mukai & Tampi 2009

### SNRI Evidence

<table>
<thead>
<tr>
<th>Authors</th>
<th>Population</th>
<th>Dose</th>
<th>Sample</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allard et al 29</td>
<td>Outpatients</td>
<td>Venlafaxine ER 75-150 mg/d [titrated] CI</td>
<td>76</td>
<td>6 mo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&amp; olpram 20-30 mg/d [titrated]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>de Vasconcelos</td>
<td>Outpatients with mild to moderate</td>
<td>Venlafaxine IR 37.5-131.25 mg/d [titrated]</td>
<td>14</td>
<td>6 wk</td>
</tr>
<tr>
<td>Cunha et al 30</td>
<td>dementia</td>
<td>Placebo</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Oslin et al 31</td>
<td>Nursing home residents</td>
<td>Venlafaxine IR 18.75-150 mg/d [titrated]</td>
<td>27</td>
<td>10 wk</td>
</tr>
<tr>
<td>Schatzberg and</td>
<td>Outpatients</td>
<td>Sertraline 25-10 mg/d</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Roose 32</td>
<td></td>
<td>Venlafaxine IR 37.5-225 mg/d [titrated]</td>
<td>104</td>
<td>8 wk</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fluoxetine 20-60 mg/d [titrated]</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td>96</td>
<td></td>
</tr>
<tr>
<td>Gast et al 33</td>
<td>Inpatients and outpatients</td>
<td>Venlafaxine ER 225-300 mg/d [titrated]</td>
<td>34</td>
<td>6 mo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nortriptyline 50-100 mg/d [titrated]</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td>Raskin et al 34</td>
<td>Outpatients</td>
<td>Duloxetine 60 mg/d [fixed dose]</td>
<td>207</td>
<td>8 wk</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td>104</td>
<td></td>
</tr>
</tbody>
</table>

Mukai & Tampi 2009
**SNRI Effectiveness**

- Dual action agents, such as TCAs and SNRIs do confer any additional efficacy benefits over SSRI’s for treatment of depression in the elderly.

  Mukai & Tampi 2009

**Atypicals For Depression**

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>All TCAS</th>
<th>Atypicals</th>
<th>Risk Ratio M: H</th>
<th>Random 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>nN</td>
<td>nN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Halkias 1995</td>
<td>1448</td>
<td>1949</td>
<td>0.75 [0.43, 1.32]</td>
<td></td>
</tr>
<tr>
<td>Hoyberg 1996</td>
<td>20/39</td>
<td>32/56</td>
<td>0.59 [0.39, 0.91]</td>
<td></td>
</tr>
<tr>
<td>Mahapatra 1997</td>
<td>0/1</td>
<td>0/1</td>
<td>0.00 [0.00, 0.00]</td>
<td></td>
</tr>
<tr>
<td>Smeraldi 1998</td>
<td>4/113</td>
<td>15/55</td>
<td>1.34 [0.82, 2.20]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>223</td>
<td>161</td>
<td><strong>0.84 [0.51, 1.38]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 76 (All TCAS), 66 (Atypicals)
Heterogeneity: Tau² = 0.13; Chi² = 6.19, df = 2 (P = 0.05); I² = 68%
Test for overall effect: Z = 0.71 (P = 0.48)

Lonergan 2009
Augmentation with Antipsychotics

- No therapeutic effects were found for haloperidol compared to placebo and trazodone & compared to risperidone and placebo
- RCTs with risperidone, olanzapine, and aripiprazole have shown modest efficacy for reducing aggression and overall agitation in AD

SSRI’s Harmless?

- Increased Risk of falls
- Deplete sodium through renal excretion
- Prolong QTC (citalopram)
• There is currently no firm evidence supporting use of antidepressants in patients with depression and dementia.
• Treatment of psychosis and agitation in patients with dementia remains a clinical challenge.
• Antipsychotics are associated with increased mortality.

Schwartz Lotters and Burns 2013

• Antidepressants are associated with a substantial risk for adverse effects, and
• Efficacy is not proven.

Schwartz Froelich & Burns 2013
**Atypical Antipsychotics**

- Serotonin Dopamine Agonists
- Multiple variable receptor activities
  - Histamine
  - Muscarinic
  - 5HT1-7
  - D1-5
  - Alpha adrenergic

**Off-Label Atypical Use with Dementia**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Strength of evidence</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Behavioral problems in dementia</td>
<td>Moderate for</td>
<td>Meta-analysis found a small benefit for risperidone and aripiprazole on agitation and psychosis outcomes.</td>
</tr>
<tr>
<td></td>
<td>• risperidone,</td>
<td>• Meta-analysis shows a possible trend toward effectiveness of olanzapine for psychosis but results did not reach statistical significance.</td>
</tr>
<tr>
<td></td>
<td>• olanzapine, and</td>
<td>• There are 3 studies of quetiapine; were too dissimilar in their design and outcomes to pool.</td>
</tr>
<tr>
<td></td>
<td>• quetiapine; Low</td>
<td>• Result in the Clinical Antipsychotic Trials of Intervention Effectiveness-Alzheimer’s Disease (CATIE-AD) showed no differences in time to discontinuation of medication between risperidone, olanzapine, quetiapine, and placebo.</td>
</tr>
<tr>
<td></td>
<td>for aripiprazole.</td>
<td>• Efficacy favored risperidone and olanzapine, and</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Tolerability outcomes favored quetiapine and placebo.</td>
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<td>• There are no studies of ziprasidone.</td>
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</tbody>
</table>

Maher et al. 2001
Typical Vs Atypical Mortality Risks

- Haloperidol (RR=1.54, 95% CI =1.38-1.73)
- Risperidone (reference risk),
- Olanzapine (RR =0.99, 95%CI=0.89-1.10),
- Quetiapine (RR=0.73, 95% CI=0.67-0.80).

• Association between mortality and antipsychotics is understood and may be due to a direct medication effect

Kales et al 2012
**Anticonvulsants in use**

- Valproic acid
- Carbamazepine
- Levetiracetam,
- Ox carbazepine,
- Topiramate and
- Zonisamide’s

*Dolder & Neely 2012*

**Stable Findings**

- Valproic acid
  - 83% develop hyperamonia *Holroyd & Overdyke, 2012*
  - Induced encephalopathy
- Carbamazepine
  - Three RCT’s indicate management of aggression and hostility *Yeh, Ouyang 2012*
Anticonvulsants Evidence Review

- Data are relatively limited.
- levetiracetam, ox carbazepine, topiramate and zonisamide's – not recommended as behavioral treatment with dementia.
  - Dolder and Neely 2012

Pretreatment Screening

- Take a good drug and alcohol history –
- Polypharmacy accounts for majority of iatrogenic morbidity.
- Antidepressant trial in older patients should last at least 6-8 weeks.
  - Continuation treatment is 12 months.
- Lithium dose ranges are lower in the elderly – 0.4-0.6 mmol/1.
Lifestyle & Pharma Aids

1. Eliminate Caffeine - including hidden forms,
   - Educate on caffeine effects - last > 24 hours and affects sleep even if taken in the morning.
2. Attempt to eliminate alcohol. In patients with dementia, remove and/or limiting amount.
3. If reflux (causing arousals; silent or with cough): avoid food and fluids 2-3 hours before HS, raising head of bed, & consider trial of antacid.

4. For allergic rhinitis (causes snoring/apnea, postnasal drip, and coughing): Try nasal steroid spray at HS, if persistent, add daytime antihistamine.
5. If suspected pain, use mattress foam topper
   - Ensure firm bed (with or without mattress topper) for back pain.
6. Schedule acetaminophen;
7. Avoid opiates.

Roth 2012
8. Circadian rhythm factors:
   – avoid or time daytime naps using hard-back chair for TV - no recliners
   – offer stimulating activities during the sleepy times
   – ensure bright light in day,
   – lower lights in evening and night,
9. Consider nighttime melatonin with morning light and strict wake time.
10. Ensure that patient does not have other primary sleep conditions that affect sleep, like RLS

11. Dose medication with sleep-disrupting effects earlier in the AM
   – (β-blockers, cholinesterase inhib., SSRIs, venlafaxine, bupropion).
   – Donepezil (Aricept) causes sleep disruption more than other cholinesterase agents.
12. Use non activating antidepressants.
13. Consider trial of switching to alternative galantamine or rivastigmine.
• 14. Dose cholinesterase inhibitor in the AM.
• 15. Nocturia: eliminate all access to fluids in 3 hours before bedtime.
• 16. Ensure that patient does not have other primary sleep conditions that affect sleep, like RLS
• 17. Nocturia: eliminate all access to fluids in 3 hours before bedtime.
• 18. Consider taking twice daily medications at dinner rather than before bed to reduce fluid load.

Non pharmacological Assistance

• A variety of non pharmacological interventions exist with demonstrated effectiveness in reducing and managing depression in the elderly.
• Many interventions focus on proactive interventions
• Several have significant impact on the magnitude of psychopharmacology used
Nursing Staff Interventions

- 1. Remove TV from the bedroom.
- 2. Ensure hands and feet are not cold at HS;
  - Suggest feet soaks, warm socks, bath.
  - Ensure that bedroom is not overly hot.
- 3. Review sleep time versus time in bed
  and

Paniagua & Paniagua 2012

- 4. Set later bedtime, and Strict wake time for mild sleep restriction.
- 5. Make clock not visible in bedroom.
- 6. Ensure that environment is free of noise and is dark at night
- 7. Have routine in place to void immediately before bed.
- 8. Dose diuretics earlier in the day if possible.

Paniagua & Paniagua 2012
EBP Summary

- 1. AD and other dementias require behavioral interventions first and then medications to treat moderate-to-severe disturbances
- 2. Nonpharmacological therapy may be inadequate in many patients
- 3. Pharmacological options are hindered by poor balance of efficacy and safety.

- 3. Better response of atypical antipsychotics for dementia patients without psychosis but adverse effects are serious
- 4. Meta-analysis, found that haloperidol was beneficial for dementia patients with aggression, not free of adverse events
  - but not for general agitation (i.e., wandering, verbal agitation, etc.).

Steinberg & Lyketesos 2012
• 5. There is no FDA-approved indication for a drug to treat psychosis or agitation in persons with dementia.
• 6. More RCTs in dementia patients with psychosis and/or agitation for atypical antipsychotics (aripiprazole, olanzapine, quetiapine, and risperidone) and for haloperidol were conducted. (Jetse et al., 2012)
• 7. RCTs examining antipsychotics for agitation and/or psychosis in dementia suggest a modest effect compared to placebo.
• 8. Individual trials have yielded negative results.
• 9. CATIE-AD trial suggested side effect burdens may negate clinical effectiveness. (Jetse et al., 2012)
• 10. Mortality is significantly higher with atypical antipsychotics than with placebo with dementia,
• 11. The FDA black-box warning identifies the risks of atypical antipsychotics.
• 12. Risk difference is 1–2% over 8–12 weeks.
• 13. In addition to acute and subacute adverse effects such as excessive sedation, postural hypotension, and falls.

Jetse et al. 2012

• 14. Atypical antipsychotics are less likely than typcals (especially haloperidol) to cause or exacerbate EPS and tardive dyskinesia.
• 15. No other differences in efficacy or safety have been demonstrated.
• 16. Individual typical or atypical drugs may have less propensity for certain side effects and should match client.

Jetse et al. 2012
17. Placebo response rate in RCTs in dementia is high (at 30–40%).
18. Nonspecific therapeutic factors; improved attention and care for patients account for a substantial of the gains in studies

**Evidence Based Needs**

- Future, prospective trials of adequate duration (i.e. at least 8-12 weeks) and of sufficient power are needed
- Systematic studies and Compilations of Studies of non pharm and pharma studies
- Use Calculated Effect Sizes
- Focusing of all Data
References


