Off-Label Use of Antipsychotics: What is the Evidence?

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Disclosures

• I am funded by AHRQ R18 HS19355-01 for education on off-label use of antipsychotics in dementia, and am also supported by HRSA (Iowa Geriatric Education Center).
• I have had no financial relationships in the past 12 months with any companies that produce proprietary products discussed in this presentation.
• Antipsychotics are generally not approved by the FDA for use in the conditions discussed today.

Objectives

• Describe changes in antipsychotic prescribing rates in the United States with the expanded use of atypical antipsychotics
• Summarize the evidence for atypical antipsychotic efficacy in off-label conditions
• Describe adverse effects of atypical antipsychotics which raise concern about increases in off-label use

Increasing Antipsychotic Use

• According to NAMCS, antipsychotic use increased from 1993-5 to 2005-9 by
  ~8 fold in children
  ~5 fold in adolescents
  ~2 fold in adults
• Why?
  Expanded indications and marketing
  Evidence in off-label indications
  Perception that atypical antipsychotics are safe

What makes an antipsychotic atypical?

• Lower risk of extrapyramidal side effects
  Parkinsonism, akathisia, dystonia, tardive dyskinesia
  Generally true, but most still have dose-dependent risk
• More effective for negative symptoms of schizophrenia?
  Evidence weak or absent with most drugs; trials biased by high dose haloperidol as a comparator
Selected Antipsychotic Risks

- Sedation
- Extrapyramidal movement disorders
- Metabolic side effects
  - Diabetes, weight gain
- Postural hypotension
- QT prolongation
- Prolactin elevation/hypogonadism
- Anticholinergic side effects
- In dementia
  - Cerebrovascular events
  - Mortality
  - Falls

Introduction to Atypical Antipsychotics

Several atypical antipsychotics are approved by the FDA for indications in addition to primary psychoses, including autism spectrum disorders, bipolar disorder, and major depressive disorder.

- Aripiprazole (Abilify®): bipolar mania, adjunct to antidepressants in major depressive disorder, irritability associated with autism
- Olanzapine (Zyprexa®): manic or mixed episodes of bipolar I, treatment-resistant or bipolar depression in combination with fluoxetine
- Quetiapine (Seroquel®): bipolar mania and bipolar depression. Quetiapine XR as adjunct to antidepressants in major depressive disorder
- Risperidone (Risperdal®): manic or mixed episodes of bipolar I; irritability associated with autism
- Prescribing of atypical antipsychotics has expanded beyond these approved indications.

Rating the Strength of Evidence From the AHRQ Comparative Effectiveness Research Review

The strength of evidence was classified into four broad categories:

- High ●●●: Further research is very unlikely to change the confidence in the estimate of effect.
- Moderate ●●: Further research may change the confidence in the estimate of effect and may change the estimate.
- Low ●: Further research is likely to change the confidence in the estimate of effect and is likely to change the estimate.
- Insufficient ○○○: Evidence either is unavailable or does not permit estimation of an effect.

Introduction to Atypical Antipsychotics

By 2001, 35.9 percent of antipsychotics prescribed to new users were of the atypical class.

As of the date of the review, nine second-generation, atypical antipsychotic drugs have been approved by the U.S. Food and Drug Administration (FDA), some for indications other than primary psychoses.

- Aripiprazole (Abilify®)
- Asenapine (Saphris®)
- Clozapine (Clozaril®, FazaClo®)
- Iloperidone (Fanapt®)
- Olanzapine (Zyprexa®)
- Paliperidone (Invega®)
- Quetiapine (Seroquel®)
- Risperidone (Risperdal®)
- Ziprasidone (Geodon®)

Summary of Studies Included in the Comparative Effectiveness Review

Off-label indications of atypical antipsychotics that have been studied and reported in the clinical literature include:

- Major depressive disorder (MDD)
- Obsessive-compulsive disorder (OCD)
- Borderline personality disorder (BPD)
- Post-traumatic stress disorder (PTSD)
- Substance abuse
- Eating disorders
- Anxiety
- Insomnia
- Dementia
- Delirium
Atypical antipsychotics increase the rate of response or remission when used as augmentation to SSRIs and SNRIs.

**Risperidone:** Strength of Evidence = Moderate

In monotherapy, quetiapine XR improves remission and response rates when compared with placebo, but olanzapine does not show efficacy.

**Strength of Evidence = Moderate**

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### Results: Atypical Antipsychotics for Major Depressive Disorder

<table>
<thead>
<tr>
<th>Atypical Antipsychotic</th>
<th>Outcome</th>
<th>Result: NNT</th>
<th>SOE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Augmentation of SSRIs/SNRIs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risperidone (3 studies)</td>
<td>YBOCS response rate</td>
<td>NNT = 5</td>
<td>Moderate</td>
</tr>
<tr>
<td>HAM-D remission rate</td>
<td>No difference from placebo.</td>
<td></td>
<td>Insufficient</td>
</tr>
<tr>
<td>HAM-D response rate</td>
<td>No difference from placebo.</td>
<td></td>
<td>Insufficient</td>
</tr>
</tbody>
</table>

**Monotherapy**

<table>
<thead>
<tr>
<th>Atypical Antipsychotic</th>
<th>Outcome</th>
<th>Result: NNT</th>
<th>SOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quetiapine XR (3 studies)</td>
<td>MADRS remission rate</td>
<td>NNT = 13</td>
<td>Moderate</td>
</tr>
<tr>
<td>MADRS response rate</td>
<td>No difference from placebo.</td>
<td></td>
<td>Insufficient</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Atypical Antipsychotic</th>
<th>Outcome</th>
<th>Result: NNT</th>
<th>SOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olanzapine (2 studies, 1,184 participants)</td>
<td>MADRS remission rate</td>
<td>No difference from placebo.</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

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### Summary of Benefits: Atypical Antipsychotics for Major Depressive Disorder

- Risperidone improves symptoms of obsessive-compulsive disorder when used as an adjunct to SSRIs for refractory patients.
  - NNT = 5
  - Strength of Evidence = Moderate

- Olanzapine and risperidone are similar in effect for augmentation of SSRIs.
  - Strength of Evidence = Low

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### Results: Atypical Antipsychotics for Obsessive-Compulsive Disorder

<table>
<thead>
<tr>
<th>Atypical Antipsychotic</th>
<th>Outcome</th>
<th>N Studies; N Participants</th>
<th>Meta-analysis Result</th>
<th>Strength of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Augmentation of SSRIs/SNRIs, Placebo Comparisons</strong></td>
<td>YBOCS score</td>
<td>3; 97</td>
<td>No difference between olanzapine and risperidone.</td>
<td>Insufficient</td>
</tr>
</tbody>
</table>

**Comparative Effectiveness for Augmentation**

<table>
<thead>
<tr>
<th>Atypical Antipsychotic</th>
<th>Outcome</th>
<th>N Studies; N Participants</th>
<th>Meta-analysis Result</th>
<th>Strength of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risperidone</td>
<td>YBOCS response rate</td>
<td>3; 97</td>
<td>NNT = 5</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

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### Summary of Benefits: Atypical Antipsychotics for Obsessive-Compulsive Disorder

- **Risperidone** improves symptoms of obsessive-compulsive disorder when used as an adjunct to SSRIs for refractory patients.
  - NNT = 5
  - Strength of Evidence = Moderate

- Olanzapine and risperidone are similar in effect for augmentation of SSRIs.
  - Strength of Evidence = Low

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### Results: Atypical Antipsychotics for Post-traumatic Stress Disorder

<table>
<thead>
<tr>
<th>Physical Disorder; Placebo</th>
<th>Outcome</th>
<th>N Studies; N Participants</th>
<th>Effect Size (Hedges’ g); Result (95% Confidence Interval)</th>
<th>Strength of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risperidone</td>
<td>Difference in CAPS</td>
<td>1; 11 (all causes)</td>
<td>Score is 6.67 points lower with risperidone (from 12.32 to 15.98 lower)</td>
<td>Moderate</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Difference in CAPS</td>
<td>1; 14 (combat-related)</td>
<td>Score is 7.95 points lower with risperidone (from 1.06 to 14.48 lower)</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

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**PTSD** = post-traumatic stress disorder

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“Using antipsychotics to treat depression is kind of like using a hammer to kill a fly. You may kill the fly, but there’s also a very good chance you’ll damage the wall.”

— Psychiatrist to remain unnamed
Stop and consider:

- Just about any sedative can improve symptoms of generalized anxiety disorder.
- Psychotherapy, meditation, breathing exercises, relaxation tapes, aerobic exercise, and many other things are also effective.
- SSRIs are a more benign first-line drug treatment, with NNT around 5. — NNT = 8 for quetiapine

Atypical Antipsychotics are Not Effective for Eating Disorders (Anorexia Nervosa)

Olanzapine and quetiapine do not increase BMI in patients with anorexia nervosa.

<table>
<thead>
<tr>
<th>Atypical</th>
<th>Outcome</th>
<th>No. Studies</th>
<th>No. Participants</th>
<th>Result and 95% CI</th>
<th>Strength of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olanzapine</td>
<td>BMI at 1 month</td>
<td>3; 84</td>
<td>NSD (BMI may lie in a range from 0.56 kg/m² to 0.57 kg/m²)</td>
<td>Moderate</td>
<td></td>
</tr>
<tr>
<td>Olanzapine</td>
<td>BMI at 3 months</td>
<td>3; 84</td>
<td>NSD (BMI may lie in a range from 0.34 kg/m² to 0.35 kg/m²)</td>
<td>Insufficient</td>
<td></td>
</tr>
<tr>
<td>Quetiapine</td>
<td>BMI at 3 months</td>
<td>1; 27</td>
<td>NSD (BMI may lie in a range from 1.74 kg/m² to 1.34 kg/m²)</td>
<td>Insufficient</td>
<td></td>
</tr>
</tbody>
</table>

10% CI: 90% confidence interval; BMI = body mass index; NSD = no statistically significant difference

Atypical Antipsychotics are Not Effective as Adjuncts in Treating Substance Abuse

<table>
<thead>
<tr>
<th>Atypical</th>
<th>Outcome</th>
<th>No. Studies</th>
<th>No. Participants</th>
<th>Effect Size/Meta-analysis Summary</th>
<th>Strength of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atypical</td>
<td>Effectiveness</td>
<td>1; 247</td>
<td>NNT = 5</td>
<td>Moderate</td>
<td></td>
</tr>
<tr>
<td>Olanzapine</td>
<td>HAM-A percent responding</td>
<td>3; 2,437</td>
<td>NNT = 8</td>
<td>Insufficient</td>
<td></td>
</tr>
<tr>
<td>Risperidone</td>
<td>HAM-A percent responding</td>
<td>1; 417</td>
<td>NSD</td>
<td>Insufficient</td>
<td></td>
</tr>
</tbody>
</table>

50% CI: 95% confidence interval; NNT = no statistically significant difference

Results and Summary of Benefits: Post-traumatic Stress Disorder

- Adjunctive treatment with risperidone reduces the symptoms of combat-related PTSD
  - Strength of Evidence = Moderate
  - Since the review, a larger (n=247) 6-month RCT in veterans found it was not effective as an adjunct to SSRIs
  - Risperidone at 2 or 4 mg and placebo.

The evidence for olanzapine and quetiapine is insufficient

- The evidence of benefits of risperidone as treatment of abused women with PTSD is insufficient
- Strength of Evidence = Insufficient

The evidence for olanzapine and quetiapine is insufficient

- Adjunctive treatment with risperidone reduces the symptoms of combat-related PTSD

Since the review, a larger (n=247) 6-month RCT in veterans found it was not effective as an adjunct to SSRIs.

Results and Summary of Benefits: Atypical Antipsychotics for Generalized Anxiety Disorder

- Quetiapine improves symptoms of generalized anxiety disorder.

<table>
<thead>
<tr>
<th>Atypical</th>
<th>Outcome</th>
<th>No. Studies</th>
<th>No. Participants</th>
<th>Effect Size/Meta-analysis Summary</th>
<th>Strength of Evidence</th>
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<td>Olanzapine</td>
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<td>NNT = 5</td>
<td>Moderate</td>
<td></td>
</tr>
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<td></td>
</tr>
</tbody>
</table>

50% CI: 95% confidence interval; NNT = no statistically significant difference
Antipsychotics in Dementia

- Some antipsychotics have modest efficacy in treating behavioral manifestations or psychosis
  - NNT = 5-14
  - Thorough evaluation and non-drug tx may reduce use
- Quetiapine has 4 negative RCTs
  - It does not work
- Antipsychotics increase risk of mortality, strokes, and other adverse events
  - Black box warning for mortality
  - NNH for mortality = 83
  - NNH for cerebrovascular adverse events = 100

Quetiapine has 4 negative RCTs
- It does not work

Antipsychotics increase risk of mortality, strokes, and other adverse events
- Black box warning for mortality
- NNH for mortality = 83
- NNH for cerebrovascular adverse events = 100

Results and Summary of Evidence: Dementia

<table>
<thead>
<tr>
<th>Antipsychotic</th>
<th>Aripiprazole</th>
<th>Olanzapine</th>
<th>Quetiapine</th>
<th>Risperidone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dementia-Overall</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Dementia-Psychosis</td>
<td>+</td>
<td>+/−</td>
<td>+/−</td>
<td>++</td>
</tr>
<tr>
<td>Dementia-Agitation</td>
<td>+</td>
<td>++</td>
<td>+/−</td>
<td>++</td>
</tr>
</tbody>
</table>

Legend:
++ = Moderate or high evidence of efficacy
+ = Low or very low evidence of efficacy
+/− = Mixed results

Results for Other Indications
- The evidence for efficacy of atypical antipsychotics is insufficient to permit conclusions for:
  - Tourette’s syndrome
  - Insomnia

Antipsychotics for Delirium
- Haloperidol has long been the standard of care
  - Low doses are often sufficient, especially in the elderly
    - E.g. < 3 mg/day; higher doses associated with more EPS
- Limited evidence supporting atypical antipsychotics
  - Risperidone and olanzapine have some evidence
  - Olanzapine is anticholinergic; use with caution
  - Quetiapine may help ‘non-cognitive’ symptoms of delirium
    - Also anticholinergic
- Discontinue on discharge/resolution

Antipsychotics for Delirium
- Emerging evidence for delirium prophylaxis
  - In high-risk elderly post-op patients
  - Starting low-dose antipsychotics prior to surgery
  - Haloperidol, risperidone, olanzapine may reduce delirium incidence or severity/duration

IA-ADAPT: Improving Antipsychotic Appropriateness in Dementia Patients
- Training and Resource Website
  - Iowa Geriatric Education Center
    - http://www.healthcare.uiowa.edu/igec/IAADAPT
  - Case-based mini-lectures
  - Pocket guides and algorithms
    - Laminated hard copies, pdfs, and mobile device apps
  - Supporting written materials
  - Dementia care online training course
  - Free CE/CME for physicians, pharmacists, nurses

Results for Delirium
- Lonergan et al, Cochrane Reviews 2007;2:Art No.:CD005594
- Tahiri et al, Psychosomatic Research 2010;69(5):485-90
- Larsen et al, Psychosomatics 2010;51:409-18
Adverse Effects of Atypical Antipsychotics

- The reviewed data were restricted to reports in studies of off-label use of atypical antipsychotics.
- With the exception of dementia, which is associated with older age, the adverse effects observed were not expected to be influenced by the diagnosis.
- Evidence was analyzed for two separate groups:
  - Elderly patients with dementia
  - Adults aged 18–64

Adverse Effects in Elderly Patients: Cardiovascular and Cerebrovascular

- Risperidone is associated with an increased risk of cerebrovascular accidents and cardiovascular adverse events.
- Olanzapine is associated with increased risk of cardiovascular adverse events.

<table>
<thead>
<tr>
<th>Comparison</th>
<th>N Studies; N Participants</th>
<th>Outcome</th>
<th>Effect Size/Meta-analytic Result: NNH</th>
<th>Strength of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risperidone vs. Placebo</td>
<td>6; 1,852</td>
<td>Cardiac events</td>
<td>One in every 54 patients treated with risperidone will experience CVA's</td>
<td>Moderate</td>
</tr>
<tr>
<td>Olanzapine vs. Placebo</td>
<td>6; 2,767</td>
<td>Cardiac events</td>
<td>One in every 34 patients treated with olanzapine will experience a cardiovascular event</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

Adverse Effects in Elderly Patients: Placebo Comparisons

- In elderly adults, extrapyramidal symptoms are common with risperidone and olanzapine.
- Atypical antipsychotics are associated with anticholinergic effects and fatigue.
- Data not shown: Atypical antipsychotics elevate the risk of arterial adverse events in elderly patients (≥65), but the evidence is too limited to permit conclusions about the degree of risk.

<table>
<thead>
<tr>
<th>Antipsychotic</th>
<th>N Studies; N Participants</th>
<th>Placebo Comparisons</th>
<th>Effect Size/Meta-analytic Result: NNH</th>
<th>Strength of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risperidone</td>
<td>5; 6,400</td>
<td>Death of 1 in every 10 patients (over a 10- to 12-week course of treatment) is attributable to treatment with an atypical antipsychotic.</td>
<td>High</td>
<td></td>
</tr>
<tr>
<td>Olanzapine</td>
<td>3; 7,200</td>
<td>Elevated risk of death with both atypical and typical antipsychotics.</td>
<td>Moderate</td>
<td></td>
</tr>
</tbody>
</table>

Adverse Effects in Adult Patients: Weight Gain/Metabolic

- The NNH for weight or appetite attributable to the intervention is lowest for clozapine. In contrast, 1 of 35 patients treated with aripiprazole show the adverse effect. The strength of evidence for this finding is high.
- Endocrine and other lab test abnormalities are not as frequently examined or detected as weight gain, although statistically significant increases when compared with placebo control groups are measurable.

<table>
<thead>
<tr>
<th>Antipsychotic</th>
<th>N Studies; N Participants*</th>
<th>NNH</th>
<th>Strength of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td>4; 799</td>
<td>24</td>
<td>Moderate</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>3; 808</td>
<td>35</td>
<td>Moderate</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>3; 1,080</td>
<td>10</td>
<td>Moderate</td>
</tr>
<tr>
<td>Risperidone</td>
<td>5; 2,182</td>
<td>24</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

Summary of Adverse Effects in Adults: Weight Gain/Metabolic

- Antipsychotics in the atypical class generally promote weight gain, but olanzapine is associated with greater risk than other atypicals.
- Olanzapine NNH = 3
- NNH = 16–35 for other atypical antipsychotics

- Some atypical antipsychotics (olanzapine in particular) are associated with endocrine and metabolic abnormalities, but the degree of increased risk is not clear.
- Risk in children was not reviewed
- But weight gain tends to be worse in most studies of antipsychotics in children
Adverse Effects in Adult Patients: Sedation and EPS

- As shown below, sedation is measurable with the use of all atypical antipsychotics studied, and fatigue may also be found.
- Extrapyramidal symptoms not found in placebo-treated groups are found with aripiprazole, quetiapine, and ziprasidone.

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>Aripiprazole</th>
<th>Clozapine</th>
<th>Quetiapine</th>
<th>Risperidone</th>
<th>Ziprasidone</th>
<th>Strength of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sedation</td>
<td>5 (1.3%)</td>
<td>36 (7.5%)</td>
<td>26 (5.2%)</td>
<td>24 (4.8%)</td>
<td>6 (1.2%)</td>
<td>Low</td>
</tr>
<tr>
<td>Fatigue</td>
<td>11 (4.1%)</td>
<td>13 (5.4%)</td>
<td>18 (7.0%)</td>
<td>14 (5.8%)</td>
<td>14 (5.8%)</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

* Adults 18–64 years of age. EPSs = extrapyramidal symptoms; NNH = number needed to harm; NSD = no statistically significant difference

Summary

- Evidence supports the use of some atypical antipsychotics in some off-label conditions  
  - But if evidence of safety and efficacy was strong, would they be FDA approved?
- Antipsychotics have significant risks  
  - Often dose-dependent
- Also consider their high cost
- The AHRQ review is an excellent source for further information  
  - www.effectivehealthcare.ahrq.gov/offlabelantipsych.cfm

Gaps in Knowledge about Off-Label Use

- Effects of age, race, ethnicity, and baseline severity of disease on outcomes is unknown
- Too few studies to permit conclusions about dosage and duration of treatment for most drugs and indications
- Few head-to-head comparisons of antipsychotics.
- Adverse event reporting is not standardized, which prevents global analysis and understanding of risks
- Evidence about the effects of antipsychotics on endocrine function, metabolism, and blood glucose regulation is limited  
  - But case reports suggest they can all cause diabetic ketoacidosis within weeks of initiation