### Results

**Psychosis, agitation, and global behavioral symptoms in dementia**

#### Efficacy

- **N = 393 studies selected**
  - n = 162 trials with efficacy outcomes
  - n = 231 trials or large observational studies with adverse events

  **NOTE:** no relevant trials included for Asenapine, Iloperidone, Paliperidone.

- **Results**
  - Psychosis
  - Agitation
  - Global behavioral symptoms

#### Inclusion criteria

- Aripiprazole
- Asenapine
- Iloperidone
- Olanzapine
- Paliperidone
- Quetiapine
- Risperidone
- Ziprasidone

#### Exclusion criteria

- Clozapine

#### Evaluation Methods for Included Studies

- Four investigators independently reviewed titles and abstracts and abstracted data on efficacy outcomes
- Pooled analysis conducted
- One investigator abstracted data on adverse events; checked by a second investigator
- Quality assessment (Jadad) on RCTs
- Strength of evidence (GRADE)
- Meta analysis: pooled random effects estimate
- OR for adverse events (>2 trials)

#### Outcomes considered:

- Efficacy in dementia
- NPI total score (global)
- Efficacy in psychosis
- NPI psychosis scale
- Efficacy in agitation
- Cohen-Mansfield agitation inventory

- Other scales if above not included in study

#### Study Selection

- **N = 38 trials**
  - Mean sample size = 238 (16 to 815)
  - Follow up = 2 days to 1 year
  - Trial quality (Jadad) = 0 to 5

- **N = 18 placebo controlled trials (pooled analysis)**
  - Follow up = 6 to 12 weeks
  - Outcomes examined:
    - Improvement in psychosis (principally delusions and hallucinations)
    - Improvement in agitation (physical aggression, verbal aggression, excitability, oppositional behaviors, excessive motor activity)
    - Total global score

#### Efficacy

- **Total global scores** = small but significant effect (mean difference; CI) for:
  - Aripiprazole vs placebo = 0.20 (0.04 to 0.35) (3 studies)
  - Olanzapine vs placebo = 0.12 (0 to 0.25) (4 studies)
  - Risperidone vs placebo = 0.19 (0.38) (6 studies)
  - Quetiapine vs placebo = 0.11 (-0.02 to 0.24) (4 studies)

- **Mean NPI total score for patients treated with antipsychotic**:
  - 35% improvement
  - Pooled NPI total score vs placebo = 3.41 points
  - Minimum clinically observable change = 3 points
  - Significant heterogeneity; no publication bias

#### Comparative Effectiveness

- **N = 3 studies**
  - Risperidone vs olanzapine
  - Risperidone vs quetiapine

- **N = 5 studies**
  - Atypical antipsychotic vs haloperidol
  - - inconsistent results

#### Generalized anxiety disorder

- **Efficacy**
  - **N = 14 studies**
  - 12 placebo controlled
  - Sample size range = 12 to 951
  - Trial quality (Jadad) = 2 to 5
  - Mean follow up = 6 to 18 weeks

- **N = 1 olanzapine**
  - N = 9 quetiapine
  - N = 3 risperidone

- **Flexible dosing**
  - Outcome assessment = HAM-A Rating Scale

- **Atypical antipsychotic vs placebo**
  - **N = 5**
  - Olanzapine trial (n = 24) favored olanzapine but NS

- Risperidone trial no statistical or clinical difference

- **Quetiapine**
  - **N = 3 studies** (N = 2437 subjects)
  - Dose range = 30 to 300 mg/d
  - 26% chance of a favorable response at 8 weeks (NNT = 8)
  - Approx effect size = 0.30

- **Significant heterogeneity; no publication bias**

- **Strength of evidence** = moderate (inconsistency of results; all studies funded by manufacturers)

- **Studies not pooled**
  - **N = 1 ziprasidone**
  - **N = 6 quetiapine**
  - **N = 2 risperidone**

- Ziprasidone = no difference vs placebo

- Risperidone = one study = better response at 8 weeks
  - one study = no response in bipolar patients

- **Quetiapine**
  - - assessed ability to quetiapine to improve response to SSRI = inconclusive results

---

### Source

### Generalized anxiety disorder (continued)

**Comparative effectiveness**

No studies directly compared atypical antipsychotics for GAD
Quetiapine 50 mg/d vs 150 mg/d vs paroxetine 20 mg/d
- equally effective at 8 weeks
- fewer sexual side effects with quetiapine
Quetiapine 150 mg/d vs 300 mg/d vs escitalopram 10 mg/d
- equally effective at 8 weeks

### Obsessive-compulsive disorder

#### Efficacy

N = 4 prior meta analyses
All found significant evidence of benefit for atypical antipsychotics

N = 16 studies (6 not included in prior systematic reviews)
n = 10 placebo controlled (augmentation for non-response to SSRIs)
Sample size range = 16 to 82
Follow up range = 6 weeks to 6 months
Trial quality (Jadad) = 1 to 5
Outcome assessment = Yale-Brown Obsessive Compulsive Scale
Response varied (25% to 35% improvement)

<table>
<thead>
<tr>
<th>Antipsychotic</th>
<th>N</th>
<th>Studies (pooled)</th>
<th>Dose range</th>
<th>Favor treated with quetiapine, but NS</th>
<th>Unexplained heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olanzapine</td>
<td>2</td>
<td>1 meta analysis</td>
<td>Mean dose = 11.2 mg/d and 6.1 mg/d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quetiapine</td>
<td>5</td>
<td>7 assessed drugs without an FDA approved indication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risperidone</td>
<td>3</td>
<td>33 studies (aripiprazole, olanzapine, quetiapine, risperidone)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Other conditions

Eating disorders
N = 1 quetiapine study
N = 5 olanzapine studies
Evidence does not support use of olanzapine

### Personality disorder

N = 1 study (N = 13 subjects)
Evidence inconclusive

### PTSD

N = 36 studies
n = 7 assessed drugs without an FDA approved indication
(NOTE: Evidence rating not specified)

### Substance use disorders

N = 33 studies (aripiprazole, olanzapine, quetiapine, risperidone)
Evidence does not support atypical antipsychotic use for SUD

### Insomnia

N = 1 study (N = 13 subjects)
Evidence inconclusive

### Sedation (vs placebo) (pooled ORs)

Aripiprazole = 2.60 (1.57 to 4.54)
Olanzapine = 4.60 (2.87 to 7.55)
Quetiapine = 5.20 (2.93 to 9.51)
Risperidone = 2.30 (1.79 to 3.05)

### Extrapyramidal symptoms (vs placebo) (pooled ORs)

Olanzapine = 15.20 (3.50 to 63.83)
Risperidone = 5.90 (1.87 to 18.30)

### Adverse Events

#### Elderly patients with dementia

2005 FDA warning = increased risk of death
N = 15 studies vs placebo (pooled OR 1.54; 1.06 to 2.23, NNH = 87

N = 2 large cohort studies
Higher mortality in patients taking antipsychotics

Pooled data vs placebo for cardiovascular symptoms, edema, and vasodilatation
No association
- quetiapine
- aripiprazole

Increased risk of stroke
- risperidone = pooled OR 3.12; 1.32 to 8.21, NNH = 53
- numbers of trials and patients were small and CIs were wide

Increase in appetite and body weight
- olanzapine = pooled OR 4.70; 1.87 to 14.14, NNH = 24
- risperidone = pooled OR 3.40; 1.08 to 12.75, NNH = 25

Development of diabetes
N = 1 (risperidone vs placebo); no difference in risk

Central and peripheral anticholinergic effects
N = 1
Olanzapine vs placebo = OR 3.30; 1.62 to 7.17, NNH = 6

### Other conditions

Eating disorders
N = 4 prior meta analyses All found significant evidence of benefit for atypical antipsychotics

N = 16 studies (6 not included in prior systematic reviews)
n = 10 placebo controlled (augmentation for non-response to SSRIs)
Sample size range = 16 to 82
Follow up range = 6 weeks to 6 months
Trial quality (Jadad) = 1 to 5
Outcome assessment = Yale-Brown Obsessive Compulsive Scale
Response varied (25% to 35% improvement)

<table>
<thead>
<tr>
<th>Antipsychotic</th>
<th>N</th>
<th>Studies (pooled)</th>
<th>Dose range</th>
<th>Favor treated with quetiapine, but NS</th>
<th>Unexplained heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olanzapine</td>
<td>2</td>
<td>1 meta analysis</td>
<td>Mean dose = 11.2 mg/d and 6.1 mg/d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quetiapine</td>
<td>5</td>
<td>7 assessed drugs without an FDA approved indication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risperidone</td>
<td>3</td>
<td>33 studies (aripiprazole, olanzapine, quetiapine, risperidone)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Other conditions

Eating disorders
N = 1 quetiapine study
N = 5 olanzapine studies
Evidence does not support use of olanzapine

#### Personality disorder

N = 12 studies
Evidence is mixed

#### PTSD

N = 1 meta analysis
N = 10 studies (risperidone or olanzapine)
Evidence is moderate for use of olanzapine

#### Substance use disorders

N = 33 studies (aripiprazole, olanzapine, quetiapine, risperidone)
Evidence does not support atypical antipsychotic use for SUD

#### Insomnia

N = 1 study (N = 13 subjects)
Evidence inconclusive

#### Sedation (vs placebo) (pooled ORs)

Aripiprazole = 2.60 (1.57 to 4.54)
Olanzapine = 4.60 (2.87 to 7.55)
Quetiapine = 5.20 (2.93 to 9.51)
Risperidone = 2.30 (1.79 to 3.05)

#### Extrapyramidal symptoms (vs placebo) (pooled ORs)

Olanzapine = 15.20 (3.50 to 63.83)
Risperidone = 5.90 (1.87 to 18.30)

#### Increase in urinary tract infections (NNH range = 16 to 36)

Risperidone = 1.60 (1.13 to 2.13)
Quetiapine = 2.40 (1.16 to 5.15)
Olanzapine = 9.50 (1.47 to 401.07)

#### Decline in cognitive function (see CATIE-AD)

Olanzapine
Quetiapine
Risperidone
**Adverse Events** (continued)  
**Elderly patients with dementia (continued)**

<table>
<thead>
<tr>
<th>Comparative harms</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 6 head-to-head trials</td>
</tr>
<tr>
<td>Neurological symptoms</td>
</tr>
<tr>
<td>Olanzapine vs risperidone</td>
</tr>
<tr>
<td>- olanzapine OR 1.54; 1.02 to 2.34</td>
</tr>
<tr>
<td>N = 6 large high quality cohort studies</td>
</tr>
<tr>
<td>n = 4 found an increased risk of death (2 = similar risk)</td>
</tr>
<tr>
<td>n = 1 found higher mortality with conventional and atypical antipsychotic medications of other psychotropic meds</td>
</tr>
</tbody>
</table>

**Nonelderly adults**

| Death, stroke, and other cardiovascular symptoms seldom assessed |
| N = 1 large cohort; age range 30 to 74 |
| - higher rates of sudden cardiac death for any antipsychotic (conventional and atypical) use vs no use |
| - risk increased with dose |
| N = 1 large cohort; age range 16 to 85 |
| - greater odds of venous thromboembolism vs no use |
| N = 85 studies for meta analysis |

| Association with weight gain |
| Olanzapine = pooled OR 11.3; 8.22 to 15.74, NNH = 3 |
| Ziprasidone = no association |

| Risk of diabetes |
| N = 1 study |
| Olanzapine = OR 5.14; 0.57 to 244.28 (NS) |

| Sedation Association with every atypical antipsychotic |
| Fatigue Association with all atypical antipsychotics except risperidone |
| Akathisia N = 5 studies |
| Aripiprazole = pooled OR 11.80; 7.40 to 19.61 |

| Extrapyramidal symptoms |
| Aripiprazole |
| Quetiapine |
| Ziprasidone |

**Adverse Events** (continued)  
**Non elderly adults (continued)**  
**Comparative harms**

| N = 1 |
| Olanzapine vs ziprasidone |
| - olanzapine OR for weight gain = 4.02; 2.25 to 7.48 |
| N = 2 |
| Quetiapine vs risperidone |
| - quetiapine associated with higher odds for decreased salivation, neurological events, sedation, and agitation |

**Comments**

This systematic review demonstrates evidence for the efficacy of atypical antipsychotic medications for only a few of the off-label conditions that are currently being treated.

Aripiprazole, olanzapine, and risperidone are associated with small but statistically significant benefits for the treatment of behavioral symptoms in dementia.

Drug doses vary, but are generally about 50% lower than those used in treating younger adults.

Three large trials demonstrated a significant benefit for quetiapine in treatment of generalized anxiety disorder.

Risperidone is associated with significant improvement in obsessive compulsive disorder.

Evidence does not support using atypical antipsychotic medications for substance use or eating disorders, or for insomnia.

The use of atypical antipsychotic medications is associated with adverse outcomes, including a small but statistically significant risk of death in elderly patients with dementia.

Other cardiovascular symptoms, sedation, fatigue, extrapyramidal symptoms, and urinary tract symptoms are also associated with some or all of the studied atypical antipsychotic medications, with the latter two occurring in up to 8% and 18% of elderly patients, respectively.

Akathisia is associated with aripiprazole use and weight gain is common with several drugs, particularly olanzapine, in which more than 40% of patients may report increased appetite or weight gain.

**Conclusion:** Benefits and harms vary among atypical antipsychotic medications for off-label use. For global behavioral symptom scores associated with dementia in elderly patients, small but statistically significant benefits were observed for aripiprazole, olanzapine, and risperidone. Quetiapine was associated with benefits in the treatment of generalized anxiety disorder, and risperidone was associated with benefits in the treatment of obsessive-compulsive disorder; however, adverse events were common.

**New evidence since 2006 (prior review):**

Numerous new trials have been sufficient to gain FDA approval for quetiapine and aripiprazole as augmentation therapy for major depressive disorder.

There is also new evidence regarding the benefit of quetiapine for treating GAD.

The strength of evidence has increased from moderate to high for the efficacy of atypical antipsychotic medications in treating behavioral symptoms in patients with dementia.

The strength of evidence had decreased from moderate to low for quetiapine in patients with OCD.

New evidence has emerged that atypical antipsychotic medications are ineffective for eating disorders and substance use disorder.