



# Effective Health Care

## Efficacy and Comparative Effectiveness of Off-Label Use of Atypical Antipsychotics

### Executive Summary

#### Background

Aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone are atypical antipsychotics approved by the U.S. Food and Drug Administration (FDA) for treatment of schizophrenia and bipolar disorder. These drugs have been studied for off-label use in the following conditions: dementia and severe geriatric agitation, depression, obsessive-compulsive disorder, posttraumatic stress disorder, and personality disorders. The atypicals have also been studied for the management of Tourette's syndrome and autism in children. The purpose of this report is to review the scientific evidence on the safety and effectiveness of such off-label uses.

The Key Questions were:

**Key Question 1.** What are the leading off-label uses of atypical antipsychotics in the literature?

**Key Question 2.** What does the evidence show regarding the effectiveness of atypical antipsychotics for off-label indications, such as depression? How do atypical antipsychotic medications compare with other drugs for treating off-label indications?

**Key Question 3.** What subset of the population would potentially benefit from off-label uses?

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**Key Question 4.** What are the potential adverse effects and/or complications involved with off-label prescribing of atypical antipsychotics?

**Key Question 5.** What are the appropriate dose and time limit for off-label indications?



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## Conclusions

Evidence on the efficacy of off-label use of atypical antipsychotics is summarized in Table A. Table B summarizes findings on adverse events and safety.

### Leading off-label uses of atypical antipsychotics

- ▶ The most common off-label uses of atypical antipsychotics found in the literature were treatment of depression, obsessive-compulsive disorder, posttraumatic stress disorder, personality disorders, Tourette's syndrome, autism, and agitation in dementia. In October 2006, the FDA approved risperidone for the treatment of autism.

### Effectiveness and comparison with other drugs

#### Dementia-agitation and behavioral disorders

- ▶ A recent meta-analysis of 15 placebo-controlled trials found a small but statistically significant benefit for risperidone and aripiprazole on agitation and psychosis outcomes. The clinical benefits must be balanced against side effects and potential harms. See "Potential adverse effects and complications" section.
- ▶ Evidence from this meta-analysis shows a trend toward effectiveness of olanzapine for psychosis; results did not reach statistical significance. The authors found three studies of quetiapine; they were too dissimilar in their design and the outcomes studied to pool.
- ▶ A large head-to-head placebo controlled trial (Clinical Antipsychotic Trials of Intervention Effectiveness-Alzheimer's Disease; CATIE-AD) concluded there were no differences in time to discontinuation of medication between risperidone, olanzapine, quetiapine, and placebo. Efficacy outcomes favored risperidone and olanzapine, and tolerability outcomes favored quetiapine and placebo.
- ▶ We found no studies of ziprasidone for treatment of agitation and behavioral disorders in patients with dementia.
- ▶ Strength of evidence = moderate for risperidone, olanzapine, and quetiapine; low for aripiprazole.

#### Depression

- ▶ We identified seven trials where atypical antipsychotics were used to augment serotonin

reuptake inhibitor (SRI) treatment in patients with initial poor response to therapy, two studies in patients with depression with psychotic features, and four trials in patients with depression with bipolar disorder.

- ▶ For SRI-resistant patients with major depressive disorder, combination therapy with an atypical antipsychotic plus an SRI antidepressant is not more effective than an SRI alone at 8 weeks.
- ▶ In two trials enrolling patients with major depressive disorder with psychotic features, olanzapine and olanzapine plus fluoxetine were compared with placebo for 8 weeks. Neither trial indicated a benefit for olanzapine alone. In one trial, the combination group had significantly better outcomes than placebo or olanzapine alone, but the contribution of olanzapine cannot be determined, as the trial lacked a fluoxetine-only comparison arm.
- ▶ For bipolar depression, olanzapine and quetiapine were superior to placebo in one study for each drug, but data are conflicting in two other studies that compared atypical antipsychotics to conventional treatment.
- ▶ We found no studies of aripiprazole for depression.
- ▶ Strength of evidence = moderate strength of evidence that olanzapine, whether used as monotherapy or augmentation, does not improve outcomes at 8 weeks in SRI-resistant depression; low strength of evidence for all atypical antipsychotics for other depression indications due to small studies, inconsistent findings, or lack of comparisons to usual treatment.

#### Obsessive-compulsive disorder (OCD)

- ▶ We identified 12 trials of risperidone, olanzapine, and quetiapine used as augmentation therapy in patients with OCD who were resistant to standard treatment.
- ▶ Nine trials were sufficiently similar clinically to pool. Atypical antipsychotics have a clinically important benefit (measured by the Yale-Brown Obsessive-Compulsive Scale) when used as augmentation therapy for patients who fail to adequately respond to SRI therapy. Overall, patients taking atypical antipsychotics were 2.66 times as likely to "respond" as placebo patients (95-percent confidence interval (CI): 1.75 to 4.03). Relative risk of "responding" was 2.74 (95-percent

CI: 1.50 to 5.01) for augmentation with quetiapine and 5.45 (95-percent CI: 1.73 to 17.20) for augmentation with risperidone. There were too few studies of olanzapine augmentation to permit separate pooling of this drug.

- ▶ We found no trials of ziprasidone or aripiprazole for obsessive-compulsive disorder.
- ▶ Strength of evidence = moderate for risperidone and quetiapine; low for olanzapine due to sparse and inconsistent results.

### **Posttraumatic stress disorder (PTSD)**

- ▶ We found four trials of risperidone and two trials of olanzapine of at least 6 weeks duration in patients with PTSD.
- ▶ There were three trials enrolling men with combat-related PTSD; these showed a benefit in sleep quality, depression, anxiety, and overall symptoms when risperidone or olanzapine was used to augment therapy with antidepressants or other psychotropic medication.
- ▶ There were three trials of olanzapine or risperidone as monotherapy for women with PTSD; the evidence was inconclusive regarding efficacy.
- ▶ We found no studies of quetiapine, ziprasidone, or aripiprazole for PTSD.
- ▶ Strength of evidence = low for risperidone and olanzapine for combat-related PTSD due to sparse data; very low for risperidone or olanzapine for treating non-combat-related PTSD.

### **Personality disorders**

- ▶ We identified five trials of atypical antipsychotic medications as treatment for borderline personality disorder and one trial as treatment for schizotypal personality disorder.
- ▶ Three randomized controlled trials (RCTs), each with no more than 60 subjects, provide evidence that olanzapine is more effective than placebo and may be more effective than fluoxetine in treating borderline personality disorder.
- ▶ The benefit of adding olanzapine to dialectical therapy for borderline personality disorder was small.

- ▶ Olanzapine caused significant weight gain in all studies.
- ▶ Risperidone was more effective than placebo for the treatment of schizotypal personality disorder in one small 9-week trial.
- ▶ Aripiprazole was more effective than placebo for the treatment of borderline personality in one small 8-week trial.
- ▶ We found no studies of quetiapine or ziprasidone for personality disorders.
- ▶ Strength of evidence = very low due to small effects, small size of studies, and limitations of trial quality (e.g., high loss to followup).

### **Tourette's syndrome**

- ▶ We found four trials of risperidone and one of ziprasidone for treatment of Tourette's syndrome.
- ▶ Risperidone was more effective than placebo in one small trial, and it was at least as effective as pimozide or clonidine for 8 to 12 weeks of therapy in the three remaining trials.
- ▶ The one available study of ziprasidone showed variable effectiveness compared to placebo.
- ▶ We found no studies of olanzapine, quetiapine, or aripiprazole for Tourette's syndrome.
- ▶ Strength of evidence = low for risperidone; very low for ziprasidone.

### **Autism**

- ▶ Just before this report was published, the FDA approved risperidone for use in autism.
- ▶ Two trials of 8 weeks duration support the superiority of risperidone over placebo in improving serious behavioral problems in children with autism. The first trial showed a greater effect for risperidone than placebo (57-percent decrease vs. 14-percent decrease in the irritability subscale of the Aberrant Behavior Checklist). In the second trial, more risperidone-treated than placebo-treated children improved on that subscale (65 percent vs. 31 percent).
- ▶ We found no trials of olanzapine, quetiapine, ziprasidone, or aripiprazole for this indication.
- ▶ Strength of evidence = low.

## Population that would benefit most from atypical antipsychotics

- ▶ There was insufficient information to answer this question. It is included as a topic for future research.

## Potential adverse effects and complications

- ▶ There is high-quality evidence that olanzapine patients are more likely to report weight gain than those taking placebo, other atypical antipsychotics, or conventional antipsychotics. In two pooled RCTs of dementia patients, olanzapine users were 6.12 times more likely to report weight gain than placebo users. In a head-to-head trial of dementia patients, olanzapine users were 2.98 times more likely to gain weight than risperidone patients. In the CATIE trial, elderly patients with dementia who were treated with olanzapine, quetiapine, or risperidone averaged a monthly weight gain of 1.0, 0.7, and 0.4 pounds while on treatment, compared to a weight loss among placebo-treated patients of 0.9 pounds per month. Even greater weight gain relative to placebo has been reported in trials of non-elderly adults.
- ▶ In two pooled RCTs for depression with psychotic features, olanzapine patients were 2.59 times as likely as those taking conventional antipsychotics to report weight gain.
- ▶ In a recently published meta-analysis of 15 dementia treatment trials, death occurred in 3.5 percent of patients randomized to receive atypical antipsychotics vs. 2.3 percent of patients randomized to receive placebo. The odds ratio for death was 1.54, with a 95-percent CI of 1.06 to 2.23. The difference in risk for death was small but statistically significant. Sensitivity analyses did not show evidence for differential risks for individual atypical antipsychotics. Recent data from the DEcIDE (Developing Evidence to Inform Decisions about Effectiveness) Network suggest that conventional antipsychotics are also associated with an increased risk of death in elderly patients with dementia, compared to placebo.
- ▶ In another recently published meta-analysis of six trials of olanzapine in dementia patients, differences in mortality between olanzapine and risperidone were not statistically significant, nor were differences between olanzapine and conventional antipsychotics.
- ▶ In our pooled analysis of three RCTs of elderly patients with dementia, risperidone was associated with increased odds of cerebrovascular accident compared to placebo (odds ratio (OR): 3.88; 95-percent CI: 1.49 to 11.91). This risk was equivalent to 1 additional stroke for every 31 patients treated in this patient population (i.e., number needed to harm of 31). The manufacturers of risperidone pooled four RCTs and found that cerebrovascular adverse events were twice as common in dementia patients treated with risperidone as in the placebo patients.
- ▶ In a separate industry-sponsored analysis of five RCTs of olanzapine in elderly dementia patients, the incidence of cerebrovascular adverse events was three times higher in olanzapine patients than in placebo patients.
- ▶ We pooled three aripiprazole trials and four risperidone trials that reported extrapyramidal side effects (EPS) in elderly dementia patients. Both drugs were associated with an increase in EPS (OR: 2.53 and 2.82, respectively) compared to placebo. The number needed to harm was 16 for aripiprazole and 13 for risperidone.
- ▶ Ziprasidone was associated with an increase in EPS when compared to placebo in a pooled analysis of adults with depression, PTSD, or personality disorders (OR: 3.32; 95-percent CI: 1.12 to 13.41).
- ▶ In the CATIE trial, risperidone, quetiapine, and olanzapine were each more likely to cause sedation than placebo (15-24 percent vs. 5 percent), while olanzapine and risperidone were more likely to cause extrapyramidal signs than quetiapine or placebo (12 percent vs. 1-2 percent). Cognitive disturbance and psychotic symptoms were more common in olanzapine-treated patients than in the other groups (5 percent vs. 0-1 percent).
- ▶ There is insufficient evidence to compare atypical with conventional antipsychotics regarding EPS or tardive dyskinesia in patients with off-label indications.

- ▶ Risperidone was associated with increased weight gain compared to placebo in our pooled analyses of three trials in children/adolescents. Mean weight gain in the risperidone groups ranged from 2.1 kg to 3.9 kg per study. Odds were also higher for gastrointestinal problems, increased salivation, fatigue, EPS, and sedation among these young risperidone patients.
- ▶ Compared to placebo, all atypicals were associated with sedation in multiple pooled analyses for all psychiatric conditions studied.

### **Appropriate dose and time limit**

- ▶ There was insufficient information to answer this question. It is a topic for future research.

### **Remaining Issues**

More research about how to safely treat agitation in dementia is urgently needed. The CATIE-AD study has substantially added to our knowledge, but more information is still necessary. We make this statement based on the prevalence of the condition and uncertainty about the balance between risks and benefits in these patients. While the increased risk of death in elderly dementia patients treated with atypical antipsychotics was small, the demonstrable benefits in the RCTs were also small. Information is needed on how the risk compares to risks for other treatments.

An established framework for evaluating the relevance, generalizability, and applicability of research includes assessing the participation rate, intended target population, representativeness of the setting, and representativeness of the individuals, along with information about implementation and assessment of outcomes. As these data are reported rarely in the studies we reviewed, conclusions about applicability are

necessarily weak. In many cases, enrollment criteria for these trials were highly selective (for example, requiring an open-label run-in period). Such highly selective criteria may increase the likelihood of benefit and decrease the likelihood of adverse events. At best, we judge these results to be only modestly applicable to the patients seen in typical office-based care.

With few exceptions, there is insufficient high-grade evidence to reach conclusions about the efficacy of atypical antipsychotic medications for any of the off-label indications, either vs. placebo or vs. active therapy.

More head-to-head trials comparing atypical antipsychotics are needed for off-label indications other than dementia.

### **Full Report**

This executive summary is part of the following document: Shekelle P, Maglione M, Bagley S, Suttorp M, Mojica WA, Carter J, Rolon C, Hilton L, Zhou A, Chen S, Glassman P. Comparative Effectiveness of Off-Label Use of Atypical Antipsychotics. Comparative Effectiveness Review No. 6. (Prepared by the Southern California/RAND Evidence-based Practice Center under Contract No. 290-02-003.) Rockville, MD: Agency for Healthcare Research and Quality. January 2007. Available at: [www.effectivehealthcare.ahrq.gov/reports/final.cfm](http://www.effectivehealthcare.ahrq.gov/reports/final.cfm).

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**Table A. Summary of Evidence-Efficacy of Off-Label Use of Atypical Antipsychotics**

| Condition                                                                                                                                                                       | Strength of evidence                                                                                                                                                                                                                                                                                          | Conclusion                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Behavioral problems in dementia                                                                                                                                                 | Moderate for risperidone, olanzapine, and quetiapine; low for aripiprazole.                                                                                                                                                                                                                                   | <ul style="list-style-type: none"> <li>• A recent meta-analysis of 15 placebo-controlled trials found a small but statistically significant benefit for risperidone and aripiprazole on agitation and psychosis outcomes.</li> <li>• Evidence from this meta-analysis shows a trend toward effectiveness of olanzapine for psychosis; results did not reach statistical significance. The authors found 3 studies of quetiapine; they were too dissimilar in their design and outcomes to pool.</li> <li>• A large head-to-head placebo controlled trial (Clinical Antipsychotic Trials of Intervention Effectiveness-Alzheimer's Disease; CATIE-AD) concluded there were no differences in time to discontinuation of medication between risperidone, olanzapine, quetiapine, and placebo. Efficacy outcomes favored risperidone and olanzapine, and tolerability outcomes favored quetiapine and placebo.</li> <li>• We found no studies of ziprasidone for agitation and behavioral disorders in elderly persons with dementia.</li> </ul> |
| Specific categories of depression: <ol style="list-style-type: none"> <li>Inadequate response to SRI</li> <li>With psychotic features</li> <li>With bipolar disorder</li> </ol> | Moderate that olanzapine, whether used as monotherapy or to augment therapy, does not improve outcomes at 8 weeks in SRI-resistant depression; low for all atypical antipsychotics for other depression indications, due to small studies, inconsistent findings, or lack of comparisons to usual treatments. | <ul style="list-style-type: none"> <li>• For SRI-resistant patients with major depressive disorder, combination therapy with an atypical antipsychotic plus an SRI antidepressant is not more effective than an SRI alone at 8 weeks.</li> <li>• In 2 trials enrolling patients with major depressive disorder with psychotic features, olanzapine and olanzapine plus fluoxetine were compared with placebo for 8 weeks. Neither trial indicated a benefit for olanzapine alone. In one trial, the combination group had significantly better outcomes than placebo or olanzapine alone, but the contribution of olanzapine cannot be determined as the trial lacked a fluoxetine-only comparison arm.</li> <li>• For bipolar depression, olanzapine and quetiapine were superior to placebo in 1 study for each drug, but data are conflicting in 2 other studies that compared atypical antipsychotics to conventional therapy.</li> <li>• We found no studies of aripiprazole for depression.</li> </ul>                                  |
| Obsessive-compulsive disorder                                                                                                                                                   | Moderate for risperidone and quetiapine; low for olanzapine due to sparse and inconsistent results.                                                                                                                                                                                                           | <ul style="list-style-type: none"> <li>• We identified 12 trials of risperidone, olanzapine, and quetiapine used as augmentation therapy in patients with OCD who were resistant to standard treatment.</li> <li>• A moderate amount of evidence from 9 trials shows that these drugs have a clinically important beneficial effect when used as augmentation therapy for patients who failed to adequately respond to SRI therapy.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |

**Table A. Summary of Evidence-Efficacy of Off-Label Use of Atypical Antipsychotics (continued)**

| Condition                                   | Strength of evidence                                                                                                                          | Conclusion                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|---------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Obsessive-compulsive disorder (continued)   |                                                                                                                                               | <ul style="list-style-type: none"> <li>We found no trials of ziprasidone or aripiprazole for obsessive-compulsive disorder.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| Posttraumatic stress disorder               | Low for risperidone for combat-related PTSD due to sparse data; very low for risperidone and olanzapine for treating non-combat-related PTSD. | <ul style="list-style-type: none"> <li>We found four risperidone and two olanzapine trials of over 6 weeks for PTSD.</li> <li>There were 3 trials enrolling men with combat-related PTSD; these showed a benefit in sleep quality, depression, anxiety, and overall symptoms when risperidone or olanzapine was used to augment therapy with antidepressants or other psychotropic medication.</li> <li>We found 3 trials of olanzapine or risperidone as monotherapy for women with PTSD; the evidence was inconclusive regarding efficacy.</li> <li>We found no studies of quetiapine, ziprasidone, or aripiprazole for PTSD.</li> </ul>                                                             |
| Personality disorders                       | Very low due to small effects, small size of studies, and limitations of trial quality.                                                       | <ul style="list-style-type: none"> <li>4 RCTs, each with no more than 60 subjects, provide evidence that olanzapine is more effective than placebo and may be more effective than fluoxetine in treating borderline personality disorder.</li> <li>The benefit of adding olanzapine to dialectical therapy for borderline personality disorder was small.</li> <li>Olanzapine caused significant weight gain in all studies.</li> <li>Risperidone was more effective than placebo for the treatment of schizotypal personality disorder in 1 small 9-week trial.</li> <li>Aripiprazole was more effective than placebo for the treatment of borderline personality in 1 small 8-week trial.</li> </ul> |
| Tourette's syndrome in children/adolescents | Low for risperidone; very low for ziprasidone.                                                                                                | <ul style="list-style-type: none"> <li>We found 4 trials of risperidone and 1 of ziprasidone for this condition.</li> <li>The little evidence available is inconclusive about the efficacy of either drug.</li> <li>We found no studies of aripiprazole, quetiapine, or olanzapine for Tourette's symptoms.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                 |
| Autism in children/Adolescents              | Low for risperidone due to sparse data.                                                                                                       | <ul style="list-style-type: none"> <li>Just before this report was published, the FDA approved risperidone for use in autism.</li> <li>Two trials of 8 weeks duration support the superiority of risperidone over placebo in improving serious behavioral problems in children with autism.</li> <li>We found no trials of olanzapine, quetiapine, ziprasidone, or aripiprazole for autism.</li> </ul>                                                                                                                                                                                                                                                                                                 |

Abbreviations: FDA = U.S. Food and Drug Administration; OCD = obsessive-compulsive disorder; PTSD = posttraumatic stress disorder; RCT = randomized controlled trial; SRI = serotonin reuptake inhibitor.

| <b>Table B. Summary of Adverse Event and Safety Findings Concerning Off-Label Use of Atypical Antipsychotics for Which There is Moderate or Strong Evidence</b> |                                                               |                                                             |                                                                                                                        |  |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------|-------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------|--|
| Side effect                                                                                                                                                     | Head-to-head trials                                           | Active control trials                                       | Placebo controlled trials                                                                                              |  |
| Mortality (dementia patients only)                                                                                                                              | Insufficient evidence of difference.                          | Insufficient evidence of difference.                        | Small but significant increased risk for atypical antipsychotics compared to placebo.                                  |  |
| Cardiovascular (not including cerebrovascular accident)                                                                                                         | Insufficient evidence of difference.                          | Insufficient evidence of difference.                        | Insufficient evidence of difference.                                                                                   |  |
| Cerebrovascular accident (dementia patients only)                                                                                                               | Insufficient evidence of difference.                          | Insufficient evidence of difference.                        | Small but significant increased risk for risperidone and olanzapine compared to placebo.                               |  |
| Extrapyramidal symptoms                                                                                                                                         | More common in olanzapine and risperidone than in quetiapine. | Insufficient evidence of difference.                        | More common in risperidone, olanzapine, aripiprazole, and ziprasidone than placebo, quetiapine insufficiently studied. |  |
| Neurological (fatigue, headaches, dizziness; excludes movement disorders)                                                                                       | Insufficient evidence of difference.                          | Insufficient evidence of difference.                        | More common in risperidone, olanzapine and aripiprazole than placebo; other drugs insufficiently studied.              |  |
| Sedation                                                                                                                                                        | Insufficient evidence of difference.                          | More common in olanzapine than mood stabilizers.            | More common in atypical antipsychotics than placebo.                                                                   |  |
| Weight gain                                                                                                                                                     | More common in olanzapine than other atypical antipsychotics. | More common in olanzapine than conventional antipsychotics. | More common in olanzapine and risperidone than placebo; other drugs insufficiently studied.                            |  |