

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



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## Preface

The Agency for Healthcare Research and Quality (AHRQ) conducts the Effective Health Care Program as part of its mission to organize knowledge and make it available to inform decisions about health care. As part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Congress directed AHRQ to conduct and support research on the comparative outcomes, clinical effectiveness, and appropriateness of pharmaceuticals, devices, and health care services to meet the needs of Medicare, Medicaid, and the State Children's Health Insurance Program (SCHIP).

AHRQ has an established network of Evidence-based Practice Centers (EPCs) that produce Evidence Reports/Technology Assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care. The EPCs now lend their expertise to the Effective Health Care Program by conducting Comparative Effectiveness Reviews of medications, devices, and other relevant interventions, including strategies for how these items and services can best be organized, managed, and delivered.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strengths and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about systematic reviews, see <http://effectivehealthcare.ahrq.gov/reference/purpose.cfm>.

AHRQ expects that Comparative Effectiveness Reviews will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. In addition, AHRQ is committed to presenting information in different formats so that consumers who make decisions about their own and their family's health can benefit from the evidence.

Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site ([www.effectivehealthcare.ahrq.gov](http://www.effectivehealthcare.ahrq.gov)) to see draft research questions and reports or to join an e-mail list to learn about new program products and opportunities for input. Comparative Effectiveness Reviews will be updated regularly.

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

## ***Executive Summary***

The Effective Health Care Program was initiated in 2005 to provide valid evidence about the comparative effectiveness of different medical interventions. The object is to help consumers, health care providers, and others in making informed choices among treatment alternatives. Through its Comparative Effectiveness Reviews, the program supports systematic appraisals of existing scientific evidence regarding treatments for high-priority health conditions. It also promotes and generates new scientific evidence by identifying gaps in existing scientific evidence and supporting new research. The program puts special emphasis on translating findings into a variety of useful formats for different stakeholders, including consumers.

The full report and this summary are available at [www.effectivehealthcare.ahrq.gov/reports/final.cfm](http://www.effectivehealthcare.ahrq.gov/reports/final.cfm)

## **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?

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?

## 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.

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

| Condition   | Strength of evidence  | Conclusion  |
|---|---|---|
| <b>Behavioral problems in dementia</b>  | 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> |
| <b>Specific categories of depression:</b><br><b>a. Inadequate response to SRI</b><br><b>b. With psychotic features</b><br><b>c. With bipolar disorder</b> | 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>                                  |
| <b>Obsessive-compulsive disorder</b>  | 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> <li>We found no trials of ziprasidone or aripiprazole for obsessive-compulsive disorder.</li> </ul>  |



| Condition  | Strength of evidence  | Conclusion   |
|--|---|--|
| <b>Posttraumatic stress disorder</b>               | 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>   |
| <b>Personality disorders</b>                       | 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> |
| <b>Tourette's syndrome in children/adolescents</b> | 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>   |
| <b>Autism in children/Adolescents</b>              | 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.

**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</b>   | <b>Head-to-head trials</b>                                    | <b>Active control trials</b>                                | <b>Placebo controlled trials</b>   |
|--|---|---|--|
| <b>Mortality (dementia patients only)</b>  | Insufficient evidence of difference.                          | Insufficient evidence of difference.                        | Small but significant increased risk for atypical antipsychotics compared to placebo.                                  |
| <b>Cardiovascular (not including cerebrovascular accident)</b>                   | Insufficient evidence of difference.                          | Insufficient evidence of difference.                        | Insufficient evidence of difference.   |
| <b>Cerebrovascular accident (dementia patients only)</b>                         | Insufficient evidence of difference.                          | Insufficient evidence of difference.                        | Small but significant increased risk for risperidone and olanzapine compared to placebo.                               |
| <b>Extrapyramidal symptoms</b>   | 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. |
| <b>Neurological (fatigue, headaches, dizziness; excludes movement disorders)</b> | Insufficient evidence of difference.                          | Insufficient evidence of difference.                        | More common in risperidone, olanzapine and aripiprazole than placebo; other drugs insufficiently studied.              |
| <b>Sedation</b>  | Insufficient evidence of difference.                          | More common in olanzapine than mood stabilizers.            | More common in atypical antipsychotics than placebo.   |
| <b>Weight gain</b>   | 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.                            |

# Introduction

## Background

Antipsychotic medications, widely used for the treatment of schizophrenia and other psychotic disorders, are commonly divided into two classes, reflecting two waves of historical development. The conventional antipsychotics--also called typical antipsychotics, conventional neuroleptics, or dopamine antagonists--first appeared in the 1950s and continued to evolve over subsequent decades, starting with chlorpromazine (Thorazine), and were the first successful pharmacologic treatment for primary psychotic disorders, such as schizophrenia. While they provide treatment for psychotic symptoms - for example reducing the intensity and frequency of auditory hallucinations and delusional beliefs - they also commonly produce movement abnormalities, both acutely and during chronic treatment, arising from the drugs' effects on the neurotransmitter dopamine. These side effects often require additional medications, and in some cases, necessitate antipsychotic dose reduction or discontinuation. Such motor system problems spurred the development of the second generation of antipsychotics, which have come to be known as the "atypical antipsychotics."

Currently, the U.S. Food and Drug Administration (FDA)-approved atypical antipsychotics are aripiprazole, clozapine, olanzapine, quetiapine, risperidone, and ziprasidone. Off-label use of the atypical antipsychotics has been reported for the following conditions: dementia and severe geriatric agitation, depression, obsessive-compulsive disorder, posttraumatic stress disorder, and personality disorders. The purpose of this Evidence Report is to review the evidence supporting such off-label uses of these agents. We were also asked to study the use of the atypical antipsychotics for the management of Tourette's Syndrome and autism in children. The medications considered in this report are those listed above; however, we have excluded clozapine, which has been associated with a potentially fatal disorder of bone-marrow suppression and requires frequent blood tests for safety monitoring. Because of these restrictions, it is rarely used except for schizophrenia that has proven refractive to other treatment.

## Dementia and Severe Geriatric Agitation

Dementia is a disorder of acquired deficits in more than one domain of cognitive functioning. These domains are memory, language production and understanding, naming and recognition, skilled motor activity, and planning and executive functioning. The most common dementias - Alzheimer's and vascular dementia - are distinguished by their cause. Alzheimer's dementia occurs with an insidious onset and continues on a degenerative course to death after 8 to 10 years; the intervening years are marked by significant disturbances of cognitive functioning and behavior, with severe debilitation in the ability to provide self-care. Vascular dementia refers to deficits of cognitive functioning that occur following either a cerebrovascular event - a stroke - leading to a macrovascular dementia, or, alternatively, more diffusely located changes in the smaller blood vessels, leading to a microvascular dementia. These (and other) dementia types commonly co-occur. Psychotic symptoms are frequent among dementia patients and include

auditory hallucinations, believing that one's personal belongings have been stolen, or believing that unknown others are cohabiting with the patient (phantom boarders). Although the cognitive deficits can be severe, it is the behavioral disturbances (such as yelling or combativeness with caregivers) that typically interfere with independent living and necessitate placement in a nursing home.

Management of dementia patients includes both behavioral and psychopharmacologic interventions. Although behavioral interventions are commonly used with dementia patients, they require the presence of trained caregivers. Psychopharmacologic treatments developed specifically for dementia include acetylcholinesterase inhibitors, which attempt to compensate for the loss of neurons that produce the neurotransmitter acetylcholine by inhibiting the enzyme responsible for its degradation. Antipsychotics, including the atypicals, have been used to control both psychotic symptoms and severe behavioral agitation in dementia.

## **Depression**

Depression refers to a potentially severe episodic disturbance of mood, with a constellation of low mood, inability to experience pleasure, sleep and appetite disturbances, loss of energy, difficulty concentrating, thoughts of guilt, worthlessness, and hopelessness, and suicidal ideation. Depression is best thought of as a symptom cluster that can appear in several different psychiatric disorders. These disorders are unipolar depression, bipolar depression, major depression with psychotic features, and depression occurring during psychotic disorders, such as schizophrenia or schizoaffective disorder. (Full descriptions of the diagnostic criteria for these disorders and others discussed in this report can be found in the latest edition of the Diagnostic and Statistical Manual of Mental Disorders, the DSM.)

Unipolar depression refers to the DSM disorder called major depressive disorder and is defined by episodes of at least a majority of the above symptoms lasting at least two weeks. A particularly severe form of major depressive disorder occurs when the depression is accompanied by psychotic symptoms such as auditory hallucinations. Current treatment guidelines for the pharmacologic treatment of major depression are expressed algorithmically as a flowchart, with later steps tried after the failure of the earlier steps.<sup>1</sup> Failure may occur for a variety of reasons, including intolerable side effects or lack of improvement after treatment of an appropriate duration. The mainstays of treatment are the antidepressants, including the serotonin reuptake inhibitors (SRIs), including citalopram, escitalopram, fluoxetine, paroxetine, and sertraline; the tricyclic antidepressants, including amitriptyline, imipramine, nortriptyline, and desipramine; and other drugs with dual reuptake inhibition or other mechanisms, including bupropion, duloxetine, mirtazapine, and venlafaxine. Other treatments used include augmenting agents, medications that are not themselves antidepressants, but that speed or improve the antidepressant activity; various psychotherapies; and electroconvulsive therapy. Because of their serotonergic effects, the atypical antipsychotics have been tested as augmenting agents. For depression with psychotic features, the recommended psychopharmacologic treatment consists of the simultaneous use of antidepressants and antipsychotics - most often atypical antipsychotics.<sup>1, 2</sup>

Bipolar depression refers to the depressed phase of bipolar disorder, a severe mental illness with mood fluctuations both below (depressed) and above (manic) the normal euthymic state. (It is also informally known as manic depression, although that term has been dropped from the official diagnostic terminology.) Treatment of the depressed phase is more complicated than the treatment of unipolar depression because one of the standard treatments for depression,

antidepressant medication, has been implicated in a mood destabilization phenomenon known as “switching,” in which the mood of a patient with bipolar depression is not restored to euthymia but moves instead into the elevated mood state of mania. The optimal treatment of bipolar depression is not yet known, but current guidelines suggest that initial treatment with a mood stabilizing agent or contemporaneous use of a mood-stabilizing agent along with an antidepressant may lower the risk of switching. Because the atypical antipsychotics have FDA approval for use as mood stabilizing agents in the treatment of manic or mixed states, they have been used in combination with antidepressants for the treatment of bipolar depression.

Depressive symptoms may also occur during primary psychotic disorders. The DSM-IV-TR discourages the separate diagnosis of major depression during schizophrenia, although it acknowledges that such comorbidity is common. A related disorder, schizoaffective disorder, combines chronic psychotic symptoms similar to schizophrenia with more pronounced episodic mood disturbances, which can resemble either major depression or bipolar disorder. Whether the antipsychotics medications used to treat primary psychotic disorders also effectively treat comorbid depression is not well known.

## **Obsessive-Compulsive Disorder**

The essential features of obsessive-compulsive disorder (OCD) are obsessions (repetitive, intrusive, unwanted thoughts, impulses, or images) and compensatory compulsive behaviors that reduce or remove the distress caused by the obsessions. A common example would involve obsessions about fears of contamination by dirt or germs, which give rise to compulsions to wash one’s hands excessively. The distress caused by the obsessions, and the time devoted to, or the dysfunction caused by, the compulsions can lead to serious psychiatric morbidity. Standard treatments include psychopharmacologic approaches using the serotonin reuptake inhibitors (SRIs), such as fluoxetine, and cognitive-behavioral therapy, which promotes a kind of learning through exposure to the feared or unpleasant stimulus and prevention of the compulsive response. Limited response to both treatments is common, and various psychopharmacologic agents, including the atypical antipsychotics, have been tested for their ability to augment SRIs.

## **Posttraumatic Stress Disorder**

Posttraumatic Stress Disorder (PTSD) describes the development of characteristic disabling symptoms following exposure to trauma such as war or rape. These symptoms are grouped into three clusters: re-experiencing (nightmares, flashbacks), avoidance and numbing (avoidance of reminders of the trauma, inability to recall the trauma, feelings of detachment, restriction of emotion), and increased arousal (anger, problems with concentration, hypervigilance, exaggerated startle response). The symptoms of PTSD span diverse psychiatric categories, and include mood, anxiety, and psychotic symptoms (including auditory hallucinations, suspicion, dissociation, and emotional withdrawal). Treatment of PTSD involves medications that address each of these classes of symptoms (including atypical antipsychotics) and cognitive-behavioral and other psychotherapies.

## **Personality Disorders**

A Personality Disorder is “an enduring pattern of inner experience and behavior that deviates markedly from the expectations of the individual’s culture, is pervasive and inflexible, has an onset in adolescence or early adulthood, is stable over time, and leads to distress or impairment.”<sup>3</sup> The current edition of the DSM defines 10 such disorders. Optimal treatment of such disorders is not well understood, although some of the disorders are the focus of active research. Because of the long-term nature of the disorders, they are often treated through psychotherapy in an attempt to facilitate long-term personality change, while psychiatric medications are thought to play a role in moderating some of the symptomatic manifestations. Only two personality disorders have been treated in clinical trials with atypical antipsychotics: schizotypal personality disorder (SPD) and borderline personality disorder (BPD).

SPD is defined by pervasive deficits in interpersonal relationships, cognitive and perceptual disturbances, and eccentric behavior. The perceptual and behavioral changes often appear similar to a mild form of schizophrenia, and there is some evidence of familial aggregation of SPD in relatives of those with schizophrenia. Because of this connection, treatment with atypical antipsychotics has been tried.

BPD’s essential characteristic is instability in interpersonal relationships, self-image, and mood, along with impulsive behavior, intense anger, and recurrent suicidal gestures or attempts. There are often severe dissociative symptoms and paranoid ideation, which may occur or worsen with stress. BPD is a significant cause of psychiatric morbidity, and, because of the increased risk for suicide, mortality. Effective treatment of BPD is an area of active research. The cornerstone of treatment is psychotherapy of various kinds, with dialectical behavior therapy and mentalization-based therapy, among others, having shown some efficacy in clinical trials.<sup>4</sup> Psychiatric medications are also commonly used, to treat both comorbid conditions, such as mood disorders, and the symptoms of BPD, although the evidence supporting such use is not strong. Because of the occurrence of psychotic symptoms, and because atypical antipsychotics have mood stabilizing properties, they are commonly tried in the treatment of BPD.

## **Tourette’s Syndrome**

Tourette’s Syndrome refers to the condition of multiple motor and vocal tics, which are rapid, recurrent, stereotyped movements. Tics of Tourette’s include eye blinking, facial grimacing, throat clearing, grunting, and, uncommonly, although most notably, coprolalia, the uttering of obscenities. The tics typically start around age six (the diagnosis requires that tics must appear by age 18). Pharmacologic treatments that have been tried include antipsychotic medications and medications from other classes, including clonidine, some of the tricyclic antidepressants, and benzodiazepines.

## **Autism**

Autism is characterized by abnormal development of social interaction and communication skills and significant restriction of activities, interests, and behaviors, with symptoms developing by age three. It is categorized as one of the pervasive developmental disorders, which also include Asperger’s disorder, and the catchall category of Pervasive Developmental Disorder Not Otherwise Specified (PDD NOS). Depending on the severity of symptoms, differentiating

autism, Asperger's disorder, and PDD NOS can be difficult, and they are occasionally grouped together for study. The primary treatment for autism is therapy for behavior modification, special education, and family counseling. Psychiatric medications are often used for symptom control; commonly used medications include antidepressants, mood stabilizers, and antipsychotics, including the atypicals.

Both Tourette's Syndrome and autism can persist into adulthood, but the evidence reviewed in this report applies only to children and adolescents.

## Scope and Key Questions

The EPC was originally asked to investigate the following questions:

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

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

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

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

Key Question 5. What is the appropriate dose and time limits for off-label indications?

Representatives of the topic nominator, the state of Washington, narrowed the scope of the project to the atypical class of antipsychotics (excluding clozapine, because of its limited use in resistant schizophrenia) in December, 2004. This nominator also narrowed the psychiatric conditions to dementia/geriatric agitation, depression, obsessive-compulsive disorder (OCD), post-traumatic stress disorder (PTSD), and personality disorders among adults and autism and Tourette's syndrome among children/adolescents.





# Methods

## Topic Development

The Agency for Healthcare Research and Quality (AHRQ) originally assigned this topic to us based on a nomination by the Department of Labor and Department of Corrections in the state of Washington. Later, we were asked by AHRQ to develop this as a comparative effectiveness report. Such reviews are being conducted by the Evidence-based Practice Centers (EPCs) for the AHRQ Effective Health Care program. These reviews are one aspect of the program, developed in response to Section 1013 of the Medical Modernization Act (MMA), which called for AHRQ to conduct a range of activities pertinent to evaluating, generating, and disseminating evidence about the comparative effectiveness of medications, devices, and other interventions. The evidence report focuses on the atypical antipsychotics (risperidone, olanzapine, quetiapine, aripiprazole, and ziprasidone) as used for the following psychiatric conditions: dementia/severe geriatric agitation, depression, obsessive-compulsive disorder (OCD), personality disorders, and post-traumatic stress disorder (PTSD). We were asked to review use in children/adolescents for autism and Tourette's syndrome if time and resources permitted.

## Search Strategy

Our library searches began in December, 2004, with a search of the Cochrane Database of Reviews of Effectiveness (DARE) and Pubmed. In early January, 2005, we followed with a search of PsycInfo and the Cochrane Central Register of Controlled Trials (CENTRAL). Search strategies are available in Appendix A.

AHRQ is dedicated to identifying as many studies as possible that are relevant to the questions for each of its systematic reviews. In order to do so, we supplemented the usual electronic database and hand searches of the literature by systematically requesting information (e.g., details of studies conducted) from pharmaceutical industry stakeholders. The Effective Health Care Program Scientific Resource Center at Oregon Health & Science University requested unpublished data from the five manufacturers of atypical antipsychotics.

In addition, several recent evidence reports related to our research subject were identified. In April, 2004, the EPC at McMaster University completed an evidence report on pharmacological treatment of dementia. We examined the references of the report and ordered any articles that we had not already identified. In December, 2004, the EPC at Oregon Health & Science University completed a drug class review on atypical antipsychotics. Although that report focused on FDA-approved uses (treatment of schizophrenia and bipolar disorder), it contained a chapter on behavioral and psychological symptoms of dementia. We reviewed this chapter and ordered any relevant studies that our literature search had not captured.

## Technical Expert Panel

This evidence report was guided by a Technical Expert Panel (TEP). We invited a distinguished group of scientists and clinicians to participate in the TEP for this report. We aimed to have at least one expert on each psychiatric condition on our TEP. TEP conference calls were held in April and May 2005.

The TEP indicated that trials less than six weeks in length should be excluded from the efficacy analyses as six weeks is an insufficient time to assess outcomes. The TEP was instrumental in deciding appropriate outcome measures for specific psychiatric conditions and identifying recently published or ongoing clinical trials. The TEP reviewed the draft evidence report and provided critical feedback.

## Study Selection

Two trained researchers reviewed the list of titles and selected articles to obtain. Each article retrieved was reviewed with a brief screening form (see Appendix B) that collected data on medication, psychiatric condition, study design, population, sample size, and study duration. Again, to be included in our evidence report, the study had to involve aripiprazole, olanzapine, quetiapine, risperidone, or ziprasidone for any of the following psychiatric conditions: dementia, severe geriatric agitation, depression, obsessive-compulsive disorder (OCD), personality disorders, posttraumatic stress disorder (PTSD), autism, or Tourette's syndrome. Only studies on humans were included. Our efficacy analyses included only controlled trials of at least 6 weeks duration. Our adverse events analyses included controlled trials of any duration and case series or cohort studies with a comparison group of more than 1,000 subjects. (We found no case control studies.) Observational studies of this size were included because they may provide evidence about the possible existence of rare adverse events that are not normally well assessed in clinical trials of more modest size.

## Data Abstraction

Data were independently abstracted by a physician and a psychiatrist trained in the critical assessment of evidence. The following data were abstracted from included trials: trial name, setting, population characteristics (including sex, age, ethnicity, and diagnosis), eligibility and exclusion criteria, interventions (dose, frequency, and duration), any co-interventions, other allowed medication, comparisons, and results for each outcome. We recorded intent-to-treat results if available. Data abstraction forms are provided in Appendix B.

For efficacy outcomes, a statistician extracted data. Efficacy outcomes abstracted are listed by condition in Table 1 below. Based on important outcomes listed by the TEP, a psychiatrist chose which outcomes were most appropriate to pool. Poolability across studies was also important; the more trials that reported an outcome measure, the more likely we were to use it in

our analysis. For each treatment or placebo arm within a trial, the sample size, mean outcome, and standard deviation were extracted. If a study did not report a follow-up mean or if a follow-up mean could not be calculated from the given data, the study was excluded from analysis. For those trials that did not report a follow-up standard deviation, we imputed one by assigning the average standard deviation from other trials that reported the standard deviation for the same outcome. If fewer than two trials were available with standard deviations, then we imputed the follow-up standard deviation by taking one-fourth the theoretical range of the scale.

**Table 1. Efficacy outcomes abstracted**

| <b>Conditions</b>             | <b>Outcome Measures</b>   |
|-------------------------------|---|
| <b>Autism</b>                 | Aberrant Behavior Checklist – <b>ABC</b><br>Childhood Autism Rating Scale   |
| <b>Dementia-agitation</b>     | Agitation-Calmness Evaluation Scale - <b>ACES</b><br>Behavioral Pathology in Alzheimer's Disease Rating Scale - <b>BEHAVE-AD</b> (subscale: aggressiveness)<br>Cohen-Mansfield Agitation Inventory - <b>CMAI</b><br>Neuropsychiatric Inventory, Nursing Home - <b>NPI-NH</b> (subscale: agitation)<br>Neuropsychiatric Inventory - <b>NPI</b> (subscale: agitation)<br>Positive and Negative Symptom Scale - <b>PANSS</b> (subscale: excitement)  |
| <b>Dementia-cognition</b>     | Mini Mental Status Exam - <b>MMSE</b><br>Alzheimer's Disease Assessment Scale - <b>ADAS</b> (cognition scale)   |
| <b>Dementia-global</b>        | Neuropsychiatric Inventory, Nursing Home - <b>NPI-NH</b> (total)<br>Neuropsychiatric Inventory - <b>NPI</b> (total)<br>Clinician's Interview-Based Impression of Change - <b>CIBIC</b><br>Empirical Behavioral Pathology in Alzheimer's Disease Rating Scale - <b>E-BEHAVE-AD</b> (total)<br>Behavioral Pathology in Alzheimer's Disease Rating Scale - <b>BEHAVE-AD</b> (total)  |
| <b>Dementia-improvement</b>   | Clinical Global Impression Scale - <b>CGI:I</b> (improvement subscale)  |
| <b>Dementia-psychosis</b>     | Neuropsychiatric Inventory, Nursing Home - <b>NPI-NH</b> (subscale: psychosis)<br>Positive and Negative Symptom Scale - <b>PANSS</b> (subscale: psychosis)<br>Behavioral Pathology in Alzheimer's Disease Rating Scale <b>BEHAVE-AD</b> (sum of paranoid and delusional ideation and hallucinations items)<br>Brief Psychiatric Rating Scale - <b>BPRS</b> (subscale: psychosis) - it is the sum of unusual thought content, paranoia(or suspiciousness), hallucinations (or hallucinatory behavior), disorganized thinking (or conceptual disorganization) |
| <b>Dementia-severity</b>      | Clinical Global Impression Scale - <b>CGI:S</b> (severity subscale)   |
| <b>Depression</b>             | Hamilton Depression Scale - <b>HAM_D</b> (HDRS)<br>Montgomery - Asberg Depression Rating Scale - <b>MADRS</b><br>Bech-Rafaelson Melancholia Scale - <b>BRMES</b><br>Depression cluster - <b>PDC</b><br>Center for Epidemiologic Studies Depression Scale - <b>CES-D</b><br>Brief Symptom Inventory - <b>BSI</b>   |
| <b>Depression-improvement</b> | Clinical Global Impression Scale - <b>CGI:I</b> (improvement subscale)  |
| <b>OCD</b>                    | Yale - Brown Obsessive Compulsive Scale - <b>YBOCS</b>  |
| <b>OCD-severity</b>           | Clinical Global Impression Scale - <b>CGI:S</b> (severity subscale)   |
| <b>PTSD</b>                   | Clinician Administered PTSD Scale - <b>CAPS</b>   |
| <b>PTSD-depression</b>        | Center for Epidemiologic Studies Depression Scale - <b>CES-D</b><br>Hamilton Depression Scale - <b>HAM-D</b><br>Beck Depression Inventory - <b>BDI</b>  |
| <b>Tourette's Syndrome</b>    | Tic Symptom Self Report – <b>TSSR</b><br>Yale Global Tic Severity Scale - <b>YGTSS</b>  |

## Adverse Events

Adverse events were recorded onto a spreadsheet that identified each trial group, the description of the adverse event from the original article, the number of subjects in each group, and the number of subjects affected. Each event was counted as if it represented a unique individual. Because a single individual might have experienced more than one event, this assumption may have overestimated the number of people having an adverse event.

If a trial mentioned a particular type of adverse event in the discussion but did not report data on that adverse event, we did not include that trial in that particular event's analysis. In other words, we did not assume an adverse event occurred unless the trial report specifically stated that some number of events were observed. By taking this approach, we may have overestimated the number of patients for whom a particular adverse event was observed. Taking the opposite tack, namely assuming a particular adverse event did not occur in any study if it was not mentioned, certainly underestimates the number of patients for whom a particular adverse event occurred.

After abstracting the data, we identified mutually exclusive groups of similar events, based on clinical expertise. For example, events that affected the head, ear, eye, nose, or throat were grouped together as HEENT. A group could contain subgroups; for example, decreased salivation, increased salivation, and eye irritation are subgroups of HEENT, with their own analyses. For each adverse-event subgroup, we report the number of trials that provided data for any event in the subgroup. We also report the total number of individuals in the medication groups in the relevant trials who were observed to have experienced the event and the total number of patients in the medication groups in those trials. We then report the analogous counts for the control groups in the relevant trials.

## Quality Assessment

To assess internal validity, we abstracted data on the adequacy of the randomization method; the adequacy of allocation concealment; maintenance of blinding; similarity of compared groups at baseline and the author's explanation of the effect of any between-group differences in important confounders or prognostic characteristics; specification of eligibility criteria; maintenance of comparable groups (i.e., reporting of dropouts, attrition, crossover, adherence, and contamination); the overall proportion of subjects lost to follow-up and important differences between treatments; use of intent-to-treat analysis; post-randomization exclusions, and source of funding. We defined loss to follow-up as the number of patients excluded from efficacy analyses, expressed as a proportion of the number of patients randomized.

To assess external validity, we recorded the number screened, eligible, and enrolled; the use of run-in and washout periods or highly selective criteria; the use of standard care in the control group; and overall relevance. Funding source was also abstracted.

To arrive at a quantitative measure, we used the Jadad scale, which was developed for drug trials. This method measures quality on a scale that ranges from 0-5, assigning points for randomization, blinding, and accounting for withdrawals and dropouts.<sup>5</sup> Across a broad array of meta-analyses, an evaluation found that trials scoring 0-2 report exaggerated results compared

with trials scoring 3-5.<sup>6</sup> The latter have been called “good” quality and the former called “poor” quality.

## Applicability

Effectiveness studies compare a new drug with viable alternatives rather than with placebo; they produce health, quality of life, and economic outcomes data under real world conditions. For example, an effectiveness trial of a new asthma drug would include asthma-related emergency room visits, the frequency and costs of physician visits, patients’ quality of life, patient compliance with the medications, acquisition costs of the medications, and frequency and costs of short-term and long-term adverse events.

Clinicians and policymakers often distinguish between the efficacy of an intervention (the extent to which the treatment works under ideal circumstances) and the effectiveness of the intervention (the extent to which the treatment works on average patients in average settings). Efficacy studies tend to be smaller, to be performed on referred patients and in specialty settings, and to exclude patients with comorbidities. Effectiveness studies are larger and more generalizable to practice. Please be aware that the vast majority of studies included in our report are efficacy studies. However, effectiveness studies are included in our analyses of adverse events.

## Rating the Body of Evidence

We assessed the overall quality of evidence for outcomes using a method developed by the Grade Working Group, which classified the grade of evidence across outcomes according to the following criteria:<sup>7</sup>

- **High** = Further research is very unlikely to change our confidence on the estimate of effect.
- **Moderate** = Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- **Low** = Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- **Very Low** = Any estimate of effect is very uncertain.

GRADE also suggests using the following scheme for assigning the “grade” or strength of evidence:

| Criteria for assigning grade of evidence   |
|--|
| <p><b>Type of evidence</b><br/> Randomised trial = high<br/> Observational study = low<br/> Any other evidence = very low</p> <p><b>Decrease grade if:</b></p> <ul style="list-style-type: none"> <li>• Serious (-1) or very serious (-2) limitation to study quality</li> <li>• Important inconsistency (-1)</li> <li>• Some (-1) or major (-2) uncertainty about directness</li> <li>• Imprecise or sparse data (-1)</li> <li>• High probability of reporting bias (-1)</li> </ul> <p><b>Increase grade if:</b></p> <ul style="list-style-type: none"> <li>• Strong evidence of association-significant relative risk of <math>&gt; 2</math> (<math>&lt; 0.5</math>) based on consistent evidence from two or more observational studies, with no plausible confounders (+1)</li> <li>• Very strong evidence of association-significant relative risk of <math>&gt; 5</math> (<math>&lt; 0.2</math>) based on direct evidence with no major threats to validity (+2)</li> <li>• Evidence of a dose response gradient (+1)</li> <li>• All plausible confounders would have reduced the effect (+1)</li> </ul> |

For this report, we used both this explicit scoring scheme and the global implicit judgment about “confidence” in the result. Where the two disagreed, we went with the lower of the two classifications.

## Data Synthesis

We constructed evidence tables displaying the study characteristics and results for all included studies (Appendix C). Trials that evaluated one atypical antipsychotic against another and provided direct evidence of comparative effectiveness are classified as “head-to-head” trials. “Active” controlled trials compare an atypical antipsychotic with another class of medication. Trials that compare atypical antipsychotics with a placebo are referred to as “Placebo” controlled trials. Finally, trials that compare an antipsychotic taken with another medication with the other medication alone were examined (referred to as augmentation trials). We provide four separate evidence tables, one for each type of study (head-to-head, active control, placebo control, and augmentation). We also include an evidence table of large case series and cohort studies identified for our adverse events analyses.

Our *a priori* analytic plan was to summarize the evidence for efficacy (versus placebo or versus conventional therapy) within condition (dementia, depression, personality disorders, etc.) and across class (all five atypical antipsychotics); the evidence of risks (adverse events) was summarized within drug (each atypical antipsychotic separately) across condition. This strategy has ample support in the literature, with many examples of drugs that demonstrate similar efficacy across a class of drugs and are then distinguished on the basis of their adverse events profile.

Because the topic nominator of this report was interested primarily in efficacy, our synthesis deals both with efficacy (do these drugs work?) and comparative effectiveness (are there differences between drugs?).

## **Efficacy and Comparative Effectiveness**

For the efficacy and comparative effectiveness analyses, we focused on controlled trials that reported outcomes with at least 6 weeks follow-up. Effect sizes were calculated for each comparison. If all trials within a condition and subgroup used the same scale, then the effect size did not need to be standardized and a mean difference was calculated. For subgroups where pooling was done across several scales, we calculated an unbiased estimate using the Hedges'  $g$  effect size.<sup>8</sup> Since most of the scales used as outcome measures in the pooled analyses are scored so that more severely symptomatic persons have higher scores, a negative effect size indicates that the atypical drug has a higher efficacy than does the comparison arm (active control or placebo arm). However, for OCD, our approach was to calculate a risk ratio for each trial based on the number of "responders" within the treatment and placebo arms, because the primary outcomes were reported this way in the original trials.

For trials that were judged sufficiently clinically similar to warrant meta-analysis, we estimated a pooled random-effects estimate<sup>9</sup> of the overall mean difference in outcome measure. The individual trial mean differences are weighted by both within-study variation and between-study variation in this synthesis. We pooled the risk ratios using the same method as above for the OCD condition. We constructed forest plots in which each individual trial mean difference is shown as a box whose area is inversely proportional to the estimated variance of the mean difference in that trial. The trial's confidence interval is shown as a horizontal line through the box. The pooled "weighted mean difference" and its confidence interval are shown as a diamond at the bottom of the plot with a dotted vertical line indicating the pooled estimate value. A vertical solid line at zero indicates no effect of medication. We also report the chi-squared test of heterogeneity  $p$ -value based on Cochran's  $Q$ <sup>8</sup> and the  $I$ -squared statistic.<sup>10</sup> A significant  $Q$  statistic or  $I^2$  values close to 100 percent represent very high degrees of heterogeneity.  $I^2$  values of 25 percent, 50 percent, and 75 percent represent low, moderate, and high heterogeneity. The numbers of trials of atypical antipsychotics for depression, dementia, and OCD were sufficient for meta-analysis. For the pooled analysis of trials of OCD, the calculations were performed on the relative risk of "responding" to the drug, so the "no effect" line is at a relative risk of 1. We also calculated Number Needed to treat (NNT) where applicable.

We assessed publication bias for each condition that was pooled. Tests were conducted using the Begg<sup>11</sup> adjusted rank correlation test and the Egger<sup>12</sup> regression asymmetry test.

All meta-analyses were conducted with Stata statistical software, version 8.2 (Stata Corp., College Station, Texas).

For groups of trials not judged sufficiently clinically similar to support meta-analysis, we performed a narrative synthesis. Trials of atypical antipsychotic drugs for PTSD, personality disorders, Tourette's syndrome, and autism were summarized narratively.

## **Adverse Events**

For reporting the data on adverse events, we treated each atypical antipsychotic separately and (in general) did not group them together as a class. However, we did summarize the findings

of other systematic reviews and meta-analyses that treated these drugs as a class. For our own analyses, we divided the study populations into three groups to make them more clinically homogeneous with respect to adverse events: dementia (elderly subjects), autism and Tourette's (children and adolescents), and everything else (adults).

For subgroups of events that occurred in two or more trials, we performed a meta-analysis to estimate the pooled odds ratio and its associated 95 percent confidence interval. Given that many of the events were rare, we used exact conditional inference to perform the pooling rather than applying the usual asymptotic methods that assume normality. Asymptotic methods require corrections if zero events are observed; generally, half an event is added to all cells in the outcome-by-treatment (two-by-two) table in order to allow estimation, because these methods are based on assuming continuity. Such corrections can have a major impact on the results when the outcome event is rare. Exact methods do not require such corrections. We conducted the meta-analyses using the statistical software package StatXact Procs v6.1 (Cytel Software, Cambridge, MA).

Any significant pooled odds ratio greater than one indicates the odds of the adverse event associated with the atypical antipsychotic is larger than the odds associated with the comparison (placebo, active control, or other antipsychotic) group. We calculated Number Needed to Harm (NNH) where this occurred. We note that if no events were observed in the comparison group, but events were observed in the intervention group, the odds ratio is infinity and the associated confidence interval is bounded only from below. In such a case, we report the lower bound of the confidence interval. If no events were observed in either group, the odds ratio is undefined, which we denote as "Not calculated (NC)" in the results tables.

## Peer Review

We requested review of the draft report from our Technical Expert Panel and various additional content and methods experts. In addition, review was performed by the Effective Health Care Program Scientific Resource Center (SRC) located at Oregon Health & Science University and by pharmaceutical companies. More than 100 articles, abstracts, and reports were submitted by these reviewers for consideration. A blinded list of peer reviewer comments and author responses has been provided to the SRC.



# Results

## Literature Flow

In total, RAND reviewers examined 2,782 titles for the draft version of this report. The electronic literature search identified 2,265 titles (Figure 1). An additional eight articles were suggested from the personal libraries of the project members. Four additional articles were suggested by our TEP members. Reference mining identified another 396 potentially relevant titles. We received scientific information packets from all five drug manufacturers; these identified an additional 109 potentially relevant titles. After review of the draft report, pharmaceutical companies submitted an additional 84 conference presentations, articles, and unpublished reports.

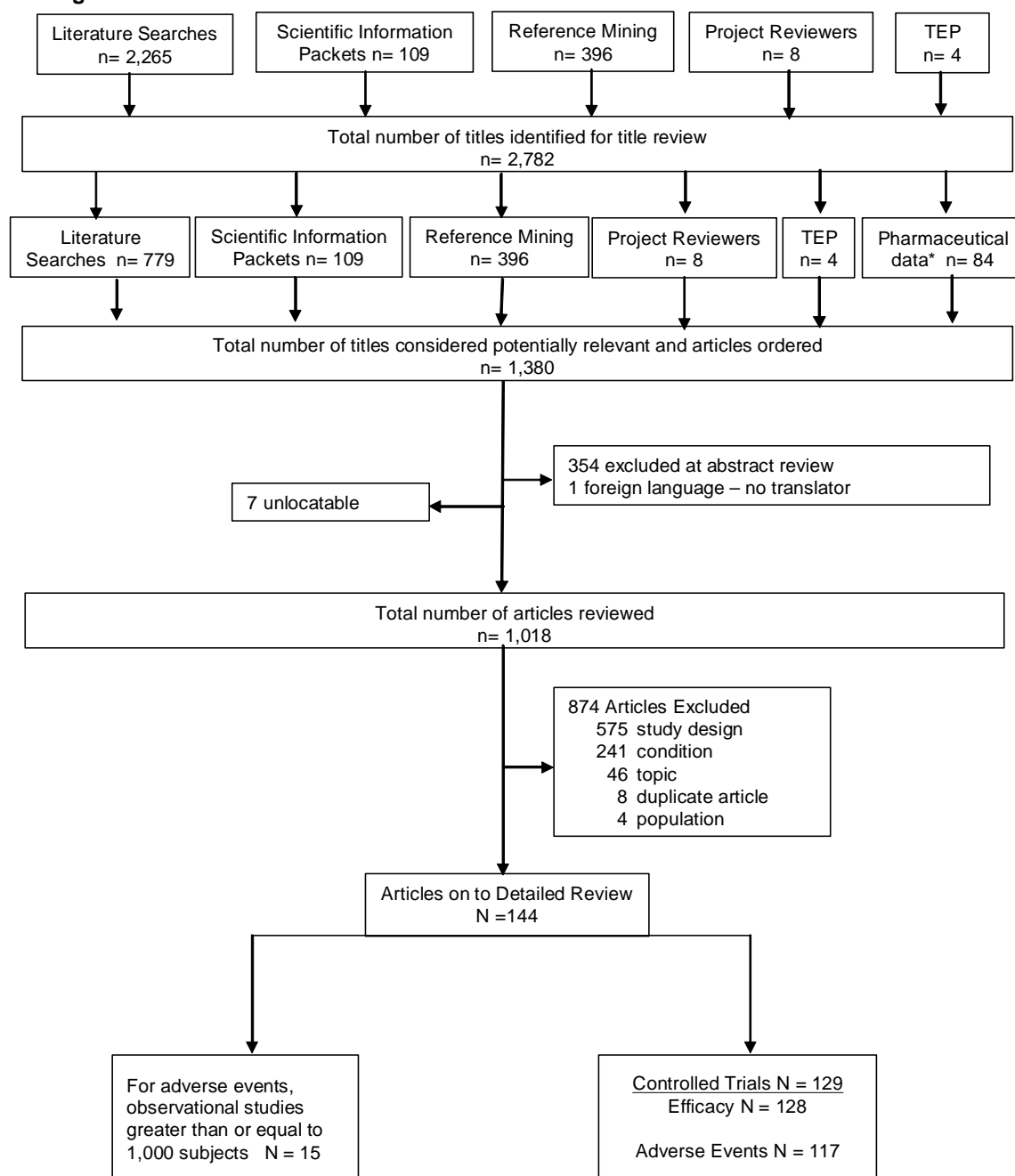
Of the titles identified through our electronic literature search, 1,486 were rejected as not relevant to our project, leaving 1,380 total from all sources. Repeat review by the research team excluded an additional 354 titles. One article, published in a foreign language was excluded due to lack of translation resources. Seven titles could not be located even after contracting with Infotrieve, a private service that specializes in locating obscure and foreign scientific publications.

Screening of retrieved articles/reports resulted in exclusion of 874: 575 due to study design; 241 had no psychiatric condition of interest; 46 did not discuss a drug (topic) of interest; eight duplicate articles- accidentally ordered; and four for population. The remaining 129 articles reporting on randomized controlled trials were reviewed in detail for efficacy and safety results. Fifteen large cases series and cohort studies were also reviewed for the safety analysis. (For a list of excluded studies, please refer to Appendix D).

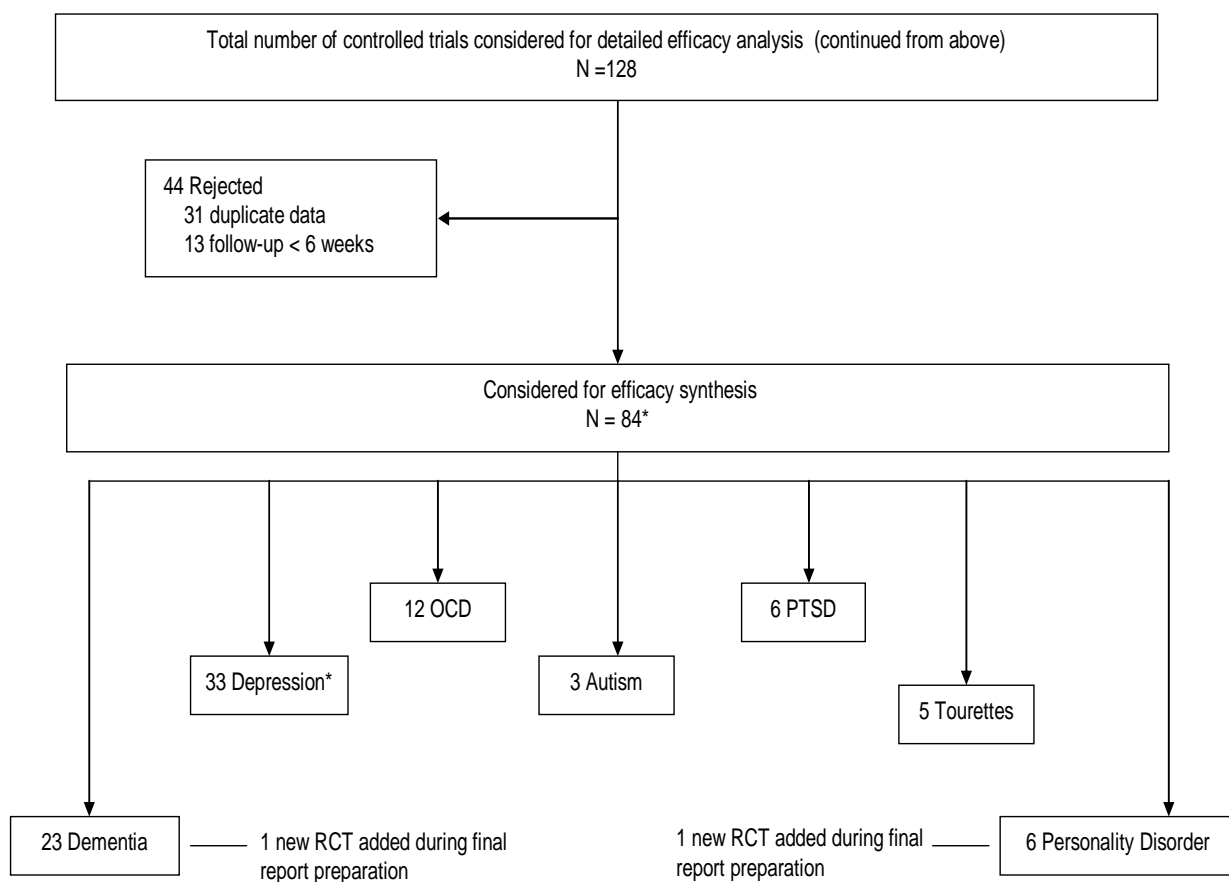
The second page of Figure 1 displays the breakdown of the 128 randomized controlled trials that reported efficacy results. Thirty-one were rejected because they represented multiple reports of many studies. We also rejected 13 reports of trials less than 6 weeks in length, per our Technical Expert Panel. The remaining 84 randomized clinical trials were reviewed for our efficacy synthesis, several of which included patients with multiple conditions. For dementia, we used a high-quality recently published meta-analyses rather than conducting our own.

As the report was being prepared for distribution, there were two RCTs newly published. One study was an assessment of aripiprazole for patients with personality disorders and the other was the Clinical Antipsychotic Trials of Intervention Effectiveness – Alzheimer’s Disease (CATIE-AD) trial.

**Figure 1. Literature Flow**



\*submitted after review of draft report



\*conditions not mutually exclusive

## Key Question #1: What are the leading off-label uses of antipsychotics in the literature?

### Key Point

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

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

### Dementia

#### Key Points

- 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.
- 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 clinically dissimilar to pool.
- A large head-to-head placebo controlled trial 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 this indication.

Schneider and colleagues recently published a meta-analysis on the efficacy and safety of atypical antipsychotics for dementia.<sup>13</sup> These same authors published an earlier meta-analysis of the risk of death with atypical antipsychotic treatment for dementia.<sup>14</sup> The new meta-analysis included only randomized, placebo controlled, double-blind parallel group trials with patients with Alzheimer's disease or dementia that assessed atypical antipsychotics marketed in the United States. This group included three trials of aripiprazole, five trials of olanzapine, three trials of quetiapine, and four trials of risperidone. The authors employed a comprehensive search for published and unpublished data, including obtaining data from abstracts presented at

meetings and from the trials' sponsors. Five trial reports were obtained via a Medline search, and 13 posters and slide presentations from medical conferences yielded an additional 10 trials. In total, the authors identified 18 placebo-controlled trials, but for three trials of risperidone, data were insufficient to be included in the meta-analysis. Of the 15 included trials, 11 were conducted in nursing home patients. The duration of trials ranged from 6 to 26 weeks, with 10 of the 15 trials being 10 or 12 weeks in duration. In total, 3,353 patients were randomized to drug and 1,757 to placebo. Overall, 87 percent of subjects were diagnosed with Alzheimer's disease. The weighted mean age was 81.2 years, and 70 percent of subjects were female. The extent of cognitive impairment ranged from mild to severe.

The authors conducted meta-analyses of separate outcomes for each drug. A summary of results is presented in Table 2. On a variety of continuous and dichotomous outcomes, including the Brief Psychiatric Rating Scale (BPRS), the NeuroPsychiatric Inventory (NPI), and the Cowen-Mansfield Agitation Inventory (CMAI), and on improvement as assessed by greater than 50 percent improvement in the total NPI score or NPI psychosis subscale, the pooled results yielded small but statistically significant effects favoring treatment with risperidone and aripiprazole. There were effects on continuous outcomes that favored treatment with olanzapine for the BPRS and the NPI, but these differences were not statistically significant. Data were insufficient to pool dichotomous outcomes for studies of olanzapine. The three studies of quetiapine were considered too clinically dissimilar to pool and results for the individual studies showed, with one exception, trends favoring treatment with quetiapine that did not reach conventional levels of statistical significance.

In the trials of risperidone, four pooled studies yielded a statistically significant effect in the Behavior Pathology and Alzheimer's Disease rating scale (Behave AD), and three pooled studies yielded a statistically significant result on the CMAI total score. With responders defined as those with greater than 50 percent improvement in Behave AD total score, three studies yielded a statistically significant odds ratio of 1.79.

In a subgroup analysis, the authors assessed the effect of atypical antipsychotics on psychosis subscales of various outcomes. In general, with the exception of three trials of risperidone assessed using the Behave AD psychosis subscale, no statistically significant results were found.

**Table 2. Pooled results of placebo-controlled trials of atypical antipsychotics for patients with dementia and behavioral disturbances or agitation**

| <b>Drug, number of trials</b> | <b>Outcome measure</b> | <b>Pooled Result<br/>Weighted mean difference</b> |
|-------------------------------|------------------------|---|
| Aripiprazole, 3 trials        | BPRS total             | -2.49 (-4.05, -0.94)                              |
|                               | NPI total              | -3.63 (-6.57, -0.69)                              |
| Aripiprazole, 2 trials        | CMAI total             | -4.05 (-6.58, -1.52)                              |
| Olanzapine, 3 trials          | BPRS total             | -0.92 (-2.48, 0.63)                               |
|                               | NPI total              | -1.74 (-4.68, 1.20)                               |
| Risperidone, 4 trials         | BEHAVE-AD total        | -1.48 (-2.35, -0.61)                              |
| Risperidone, 3 trials         | CMAI total             | -3.00 (-4.22, -1.78)                              |

| Drug, number of trials | Outcome measure  | Fixed effects odds ratio               | NNT                       |
|------------------------|--|--|---------------------------|
| Aripiprazole, 3 trials | >50% Improvement in NPI total<br>>50% Improvement in NPI psych | 1.50 (1.14, 1.99)<br>1.38 (1.04, 1.83) | 10 (6, 27)<br>14 (7, 156) |
| Risperidone, 3 trials  | >50% Improvement BEHAVE-AD total                               | 1.79 (1.37, 2.33)                      | 7 (5, 13)                 |
| Risperidone, 2 trials  | Much/Very Much Improved CGI-C                                  | 2.01 (1.49, 2.72)                      | 6 (4, 10)                 |

In other subgroup analyses that combined results across drugs, there were larger effect sizes in patients without psychosis than those with psychotic symptoms. In additional subgroup analyses, the effect size for nursing home patients was almost 10 times the effect size for community living patients (0.19 and 0.02, respectively). Also, larger effects were found in the trials of patients with a lower mean Mini Mental Status Exam (MMSE) score than in the trials with patients with a higher mean score (almost three times the effect size). Interestingly, a pooled analysis of 14 trials, across drugs, yielded an effect size of a composite outcome of -0.16 (95 percent CI, -0.08, -0.24). There was marked heterogeneity, so pooled results must be interpreted with caution.

The authors note that all of the significant improvements were small, usually less than a quarter of a standard deviation. They also note that the clinical significance of these effect sizes is uncertain, as there is debate among clinicians about the importance. A limitation of the data is the drop-out rates: approximately one-third across all trials. The authors note that these efficacy data need to be balanced against the possibility of adverse effects, including death. Information on these effects is provided in our adverse events section. They conclude that “antipsychotics are modestly effective when used judiciously and there are no demonstrated, effective pharmacological alternatives.”

In addition to the meta-analysis of placebo-controlled trials, we found four head-to-head comparisons of risperidone and olanzapine.<sup>15-18</sup> Two of the studies reported no substantive differences in efficacy between drugs among elderly patients with dementia and behavioral disturbances in 494 patients<sup>16</sup> and in 20 patients.<sup>15</sup> Differences were reported in the types of adverse effects reported, to be discussed in more detail in that section of this report. One study, reported in abstract form only,<sup>17</sup> assessed 29 patients with Alzheimer’s dementia who were randomized to olanzapine, risperidone, or placebo, for 6 weeks. This study reported that olanzapine patients had greater improvements on certain outcome measures of tension, agitation, and resistiveness, but the results are presented in insufficient detail to draw conclusions. The last study in this group compared blood assays of anticholinergic activity in 86 patients with dementia and psychosis, randomized to olanzapine or risperidone treatment, but found no statistically significant differences between treatment groups.<sup>18</sup>

A recent large RCT was published that directly compared the atypical antipsychotics risperidone, olanzapine, and quetiapine to each other and to placebo.<sup>19</sup> The Clinical Antipsychotic Trials of Intervention Effectiveness – Alzheimer’s Disease (CATIE-AD) study randomized 421 outpatients with DSM-IV criteria for Alzheimer’s type dementia or probable Alzheimer’s Disease to risperidone (average dose 1.0 mg/day), olanzapine (average dose 5.5 mg/day), quetiapine (average dose 56.5 mg/day) or placebo. The CATIE-AD trial was designed as a “pragmatic” trial to mimic real world use, and the primary endpoint was discontinuation of the drug for either lack of efficacy or troublesome side effects. Patients enrolled had a mean age

of 78 years, were 56 percent female, 79 percent white, and 73 percent of participants lived in their own home. The mean Mini-Mental Status Exam score was 15. There were no statistically significant differences between groups in the time to discontinuation of the drug (ranging from 5.3 to 8.1 weeks). More patients discontinued quetiapine or placebo than olanzapine or risperidone due to lack of efficacy, and more patients discontinued olanzapine, risperidone, or quetiapine than placebo due to troublesome side effects. At 12 weeks, efficacy measured by the Clinical Global Impression of Change did not vary between groups, but the secondary outcomes of the Neuropsychiatric Inventory and the Brief Psychiatric Rating Scale showed greater improvements in the active-treated patients than in the placebo-treated patients (but statistical tests of differences between groups were not reported). Sedation was much more common in active-treated patients than placebo. Risperidone and olanzapine were associated with much more extrapyramidal signs or Parkinsonism than placebo or quetiapine, as were confusion and mental status changes. Although not reaching conventional statistical significance, the proportion of patients gaining more than 7 percent of body weight was twice as high in risperidone and olanzapine treated patients compared to those treated with quetiapine or placebo. Cerebrovascular accidents and deaths were uncommon in all groups.

We also found five additional active-controlled trials for dementia. Three trials compared risperidone with the conventional antipsychotic haloperidol.<sup>20-22</sup> One of these studies<sup>22</sup> was a cross-over trial. Sample sizes were 58, 120, and 344 subjects. In general, there were few reported differences in efficacy between groups in these trials. Two other trials assessed the effect of adding an atypical antipsychotic to treatment with rivastigmine.<sup>23, 24</sup> One of these trials assessed risperidone<sup>23</sup> and the other assessed quetiapine.<sup>24</sup> Both trials were relatively small, enrolling 65 and 80 patients, respectively. The trial of risperidone did not find any substantial benefit of adding this drug to rivastigmine, but did conclude there was no evidence of increased adverse events with their co-administration. The study of quetiapine found that neither this drug nor rivastigmine were effective in the treatment of agitation in people with dementia in institutional care. Furthermore, this paper reported that treatment with quetiapine was associated with a significantly greater cognitive decline than was treatment with placebo at 26 weeks, as assessed by the severe impairment battery.

## Summary

In summary, a moderate amount of evidence from a prior meta-analysis and a new head-to-head and placebo-controlled trial suggests that the atypical antipsychotics risperidone, olanzapine, quetiapine and aripiprazole have small but significant benefits in improving a variety of symptoms in patients with dementia who have agitation or behavioral disturbances. The clinical benefits of these drugs are counterbalanced by troublesome side effects prompting discontinuation. The balance between benefits and harms is about equivalent in a population of patients, but may be distinctly tilted in one direction or the other in individuals. We found no studies of ziprasidone for this indication.

There is insufficient evidence to conclude that atypical antipsychotics are any more effective than conventional antipsychotics at controlling agitation and psychosis in dementia patients. There is evidence that adding the atypical antipsychotic quetiapine to rivastigmine produces no additional benefit. There is no consistent evidence that there are any appreciable differences in efficacy between risperidone, olanzapine and quetiapine. The overall strength of evidence for risperidone, olanzapine and quetiapine and outcomes is considered moderate, based on

heterogeneity, and that future research is likely to have an important impact on our confidence in the estimate of the effect and may change the estimate. The overall strength of evidence for aripiprazole is considered low, due to sparseness of data and heterogeneity.

## Depression

### Key Points

- For serotonin reuptake inhibitor (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.
- We found only two trials of atypical antipsychotics as primary therapy for major depressive disorder with psychotic features. Olanzapine and olanzapine plus fluoxetine were compared with placebo for 8 weeks in both trials. The combination group had significantly better outcomes in the first trial; in the second trial, there were no differences between groups.
- Evidence is sparse and conflicting regarding atypical antipsychotics as primary therapy for bipolar depression, compared with conventional therapy.
- We found no studies of aripiprazole for depression.

Our literature search identified 60 reports of RCTs where an outcome measure was depression.<sup>16, 25-83</sup> We rejected six of these studies because treatment duration was less than 6 weeks.<sup>48-53</sup> Many of the remaining trials assessed conditions outside the scope of this report, such as schizophrenia or schizoaffective disorder, or included mixed populations where the majority of patients had schizophrenia or schizoaffective disorder, and depression was often a secondary outcome.<sup>25, 29, 31, 34, 35, 39, 41, 46, 54-64</sup> Other studies reporting depression outcomes included bipolar disorder and acute mania;<sup>32, 65</sup> maintenance of remission in bipolar disorder;<sup>37, 38, 40, 66, 67</sup> trials with obsessive-compulsive disorder patients;<sup>68-71</sup> trials of PTSD patients;<sup>45, 72, 73</sup> and trials of dementia patients.<sup>16, 74</sup> One study of atypical antipsychotics for generalized anxiety disorder reported depression outcomes.<sup>33</sup> These studies are also beyond the scope of this report. We focused our synthesis on trials of atypical antipsychotics in three conditions: as augmentation therapy for patients with treatment-resistant depression; for the primary treatment of patients with major depression with psychotic features; and as primary for patients with bipolar disorder who are experiencing a phase of depression.

### *Augmentation therapy in patients with treatment-resistant depression*

We identified nine reports of the use of an atypical antipsychotic as augmentation therapy for patients with treatment-resistant depression.<sup>30, 43, 44, 47, 75-79</sup> Two reports were of the same study, one in abstract form<sup>75</sup> and the other as a peer-reviewed journal article;<sup>47</sup> and one abstract was a subgroup analysis of a trial presented in another abstract, leaving seven unique trials. Four reports were in peer-reviewed journals,<sup>30, 47, 76, 77</sup> but three trial outcomes were published as abstracts only.<sup>78, 43, 44, 79</sup> The salient features of these studies are presented in Table 3.



**Table 3. Trials of atypical antipsychotics as augmentation therapy for major depression**

| Author, Year                | Subjects   | N   | Treatments  | Duration | Outcomes  |
|-----------------------------|--|-----|---|----------|---|
| Shelton, 2001 <sup>47</sup> | DSM-IV criteria for recurrent major depression without psychotic features, resistant to conventional antidepressant therapy; HAM-D score of > 20; and non-response in a 6-week lead-in phase with fluoxetine   | 28  | Olanzapine (mean dose = 12.5 mg/day)<br><br>Fluoxetine (mean dose = 52 mg/day)<br><br>Olanzapine (mean dose = 13.5 mg/day) + fluoxetine (mean dose = 52 mg/day)<br><br>Placebo                                    | 8 weeks  | Olanzapine and fluoxetine resulted in significantly greater improvements on the HAM-D scale than olanzapine alone, but were not significantly better than fluoxetine alone. Combination therapy was also significantly better than either monotherapy in improvements on the MADRS. |
| Shelton, 2005 <sup>76</sup> | DSM-IV criteria for unipolar, non-psychotic major depressive disorder and at least 1 past treatment failure with an SRI with at least 4 weeks of therapy at a therapeutic dose; and non-response to a 7-week lead-in phase with nortriptyline.   | 500 | Olanzapine (mean dose = 8.3 mg/day)<br><br>Olanzapine (mean dose = 8.5 mg/day) + fluoxetine (mean dose = 35.6 mg/day)<br><br>Fluoxetine (mean dose = 35.8 mg/day)<br><br>Nortriptyline (mean dose = 103.5 mg/day) | 8 weeks  | No significant differences among groups at 8 weeks in MADRS. Significantly greater improvements for combination therapy at weeks 2-4.   |
| Corya, 2005 <sup>77</sup>   | DSM-IV criteria for major depressive disorder, single episode or recurrent, without psychotic features; with a CGI-severity score of 4 or greater; documented history of failure to achieve satisfactory response to at least 6 weeks of SRI therapy at therapeutic doses; and non-response to a 7-week lead-in phase with venlafaxine | 483 | Olanzapine + Fluoxetine in several different doses<br><br>Olanzapine (mean dose = 7.9 mg/day)<br><br>Fluoxetine (mean dose = 37.5 mg/day)<br><br>Venlafaxine (mean dose = 275.4 mg/day)                           | 12 weeks | No significant difference between combination therapy and any other group except olanzapine alone in MADRS at 12 weeks. Significantly greater improvements for combination therapy at weeks 2-6.  |

HAM-D = Hamilton Depression Scale

HAM-A = Hamilton Anxiety Scale

MADRS = Montgomery – Asberg Depression Rating Scale

**Table 3. Trials of atypical antipsychotics as augmentation therapy for major depression**

| Author, Year                  | Subjects   | N   | Treatments   | Duration | Outcomes  |
|-------------------------------|--|-----|--|----------|---|
| Yargic, 2004 <sup>30</sup>    | DSM-IV criteria for major depression and HAM-D scores or HAM-A scores indicating depression and anxiety  | 112 | Paroxetine (mean dose = 28 mg/day)<br><br>Paroxetine (mean dose = 27mg/day) + Quetiapine (mean dose “about” 60 mg/day at the end of the study).        | 8 weeks  | No difference between groups in mean HAM-D or HAM-A score at week 8, but a suggestion that improvement was faster in patients treated with combination therapy.   |
| Levitt, 2004 <sup>44</sup>    | “unipolar non-psychotic major depression” and failed an adequate trial of an SRI or venlafaxine  | 43  | Risperidone added to antidepressant<br><br>Olanzapine added to antidepressant  | 6 weeks  | No difference between groups for HAM-D.   |
| Dunner, 2003 <sup>78</sup>    | Major depression without psychotic features and a history of non-response to an adequate trial of at least 4 weeks of antidepressant therapy; a minimum MADRS score of 20; and non-response to a run-in period with sertraline   | 64  | Sertraline (100-200 mg/day)<br><br>Sertraline (100-200 mg/day) + Ziprasidone (80 mg/day)<br><br>Sertraline (100-200 mg/day) + Ziprasidone (160 mg/day) | 8 weeks  | Comparisons across groups were not presented, but when stratified by a history of non-response (SRI or non-SRI), only those patients who had a prior history of non-SRI treatment resistance showed an improvement in MADRS score at 8 weeks. |
| Gharabawi, 2004 <sup>43</sup> | DSM-IV diagnosis of major depressive disorder, single or recurrent episode; 98% did not have psychotic features; failure to respond to other antidepressants given at adequate doses for at least 6 weeks; with non-response in a 4-6 week lead-in phase with citalopram | 386 | Citalopram<br><br>Citalopram + risperidone (flexible dose)   | 24 weeks | No data on initial response to therapy; suggestion of a benefit in terms of time to relapse (102 days v. 85 days).  |

HAM-D = Hamilton Depression Scale

HAM-A = Hamilton Anxiety Scale

MADRS = Montgomery – Asberg Depression Rating Scale

Three trials assessed the effect of the combination of olanzapine and fluoxetine (augmentation of fluoxetine with olanzapine),<sup>47, 76, 77</sup> one trial each assessed the effect of augmentation of various SRIs with risperidone,<sup>43, 79</sup> ziprasidone,<sup>78</sup> and quetiapine,<sup>30</sup> and one study assessed adding risperidone or olanzapine to antidepressant therapy.<sup>44</sup> The olanzapine studies also assessed its efficacy as monotherapy. The duration of trials was from 8 to 24 weeks. The quality of most trials was fair, with only three of seven scoring 3 or greater on the Jadad scale. All trials studied patients with DSM-IV criteria for major depressive disorder, and patients with psychotic features were either excluded or constituted only a tiny fraction of enrolled patients. Some trials also required enrolled patients to exceed a certain threshold for depressive symptoms, as listed in Table 3. Almost all trials had a lead-in phase of several weeks during which patients received an antidepressant (when specified, either an SRI or venlafaxine), and only patients with an inadequate response were subsequently randomized to receive atypical antipsychotic therapy or placebo.

Most trials measured response in terms of a standardized instrument, such as the Hamilton Depression Scale (HAM-D) or the Montgomery-Asberg Depression Rating Scale (MADRS). In general, these trials found that olanzapine alone was no better than placebo in improving symptoms at 6 or 12 weeks. Also, the combination of olanzapine and fluoxetine was no better than fluoxetine alone in improvement of depressive symptoms at 8 weeks, but three trials reported more rapid improvement in depressive symptoms (at 2-4 weeks) with combination therapy using olanzapine or quetiapine. One trial presented as an abstract assessed 386 patients with depression who were nonresponders to 4-6 weeks of therapy with citalopram.<sup>43, 79</sup> These patients were randomized to receive augmentation therapy with either placebo or risperidone (mean modal dose of 1.2 mg/day) for 4-6 weeks followed by a maintenance phase of 24 weeks. The study did not report differences between groups in achieving a response to therapy, but did report that patients maintained on risperidone had a significantly longer period of time to relapse compared to placebo (102 days v. 85 days). The one trial that directly compared augmentation therapy between olanzapine and risperidone reported no differences in outcome.<sup>44</sup>

### *Major depression with psychotic features*

We identified two reports in which atypical antipsychotic therapy was used in patients with depression and psychosis.<sup>26, 80</sup> Both described the same study, one in abstract form<sup>80</sup> and the other as a peer reviewed publication.<sup>26</sup> Olanzapine and the combination of olanzapine plus fluoxetine were compared to placebo in two different 8-week trials, including 124 and 125 patients respectively, who were hospitalized for major depression with psychotic features.<sup>26, 80</sup> The numbers of men and women were nearly equal; average age was 41 years. The combination of fluoxetine and olanzapine produced significantly greater improvement than placebo or olanzapine alone in the HAM-D-24 total score at 8 weeks in the first trial,<sup>26</sup> and when classified as dichotomously as “responders,” or “non responders” a similar result was seen. The second trial found no differences between groups.

### *Bipolar depression*

We identified seven reports of trials where atypical antipsychotics were used in patients with depression and bipolar disorder.<sup>27, 28, 36, 42, 81-83</sup> One trial was reported as both an abstract<sup>81</sup> and a peer-reviewed journal article.<sup>28</sup> Another peer-reviewed paper was a subgroup analysis of this

same trial.<sup>27</sup> One additional trial was published in a peer-reviewed journal,<sup>36</sup> and the remaining three trials were reported in abstract form only.<sup>42, 82, 83</sup> Two of these abstracts reported on the same trial.<sup>82, 83</sup> Thus, there were four unique trials.

One trial<sup>27</sup> compared an 8-week course of placebo, olanzapine alone, or the combination of olanzapine and fluoxetine in 833 patients with DSM-IV criteria for bipolar depression (and at least one prior manic or mixed episode) and a MADRS score of at least 20.<sup>28, 81</sup> A second trial assessed the effect of a 12-week course of risperidone, paroxetine, or the combination when added to a mood stabilizer in 30 patients with bipolar depression, a HAM-D score of at least 18, and a score on the Young Mania Rating Scale of 8 or below.<sup>36</sup> A third trial, presented only in abstract form, assessed the effects of an 8-week course of quetiapine compared to placebo in 542 patients with DSM-IV criteria for bipolar depression who had a HAM-D score of 20 or greater and a Young Mania Rating Scale score of 12 or less.<sup>42</sup> The fourth trial, also available only in abstract form, reported the results of acute<sup>83</sup> and long-term treatment<sup>82</sup> of 410 patients with bipolar depression, a MADRS score of 20 or greater, a Clinical Global Impression severity score of four or greater, and a Young Mania Rating Scale of less than 15. Treatment was either combination therapy with olanzapine and fluoxetine or lamotrigine. In general, these trials showed that olanzapine and quetiapine are more effective than placebo for treating bipolar depression but found no evidence that risperidone is more effective than paroxetine. In the study that was presented in two abstracts, the combination of olanzapine and fluoxetine had small but significant advantages over lamotrigine in several outcome measures, including the Clinical Global Impression – severity scale, the MADRS total score, and the Young Mania Rating Scale. However, there was no significant benefit in other outcome measures (proportion of patients with a 50 percent reduction in MADRS or reaching certain thresholds).

## Summary

In patients with major depression who are resistant to SRI antidepressants, there is a modest amount of evidence that the addition of an atypical antipsychotic to an SRI is no more effective at 8 or 12 weeks than an SRI alone. Three trials support the finding that initial improvement (at 2-4 weeks) may be better with combination therapy. The data are sparse and conflicting about the efficacy of atypical antipsychotics for patients with major depression with psychotic features compared to conventional therapy. Sparse data support the superiority of olanzapine and quetiapine compared with placebo in treating bipolar depression, but data are conflicting regarding efficacy compared with conventional therapy. The only head-to-head study that compared olanzapine with risperidone as augmentation therapy for SRI-resistant major depression reported no differences. The overall quality of evidence for all depression outcomes and conditions is low, based on sparse data, heterogeneity, and that future research is likely to have an important impact on our confidence in the estimate and is likely to change the estimate.

## Obsessive-Compulsive Disorder

### Key Points

- We found several studies of risperidone, olanzapine, and quetiapine for this indication.
- Evidence from nine trials supports the finding that these three drugs have a clinically important beneficial effect when used as augmentation therapy for patients who fail to adequately respond to SRI therapy.
- The evidence of benefit is stronger for risperidone and quetiapine than for olanzapine.
- We found no studies of ziprasidone or aripiprazole.

Our literature search identified 12 trials of atypical antipsychotics for OCD.<sup>68, 69, 71, 84-92</sup> Of these, six trials assessed risperidone<sup>68, 84-88</sup> two trials assessed olanzapine,<sup>89, 92</sup> and four trials assessed quetiapine.<sup>69, 71, 90, 91</sup> All RCTs assessed the use of an atypical antipsychotic medication as augmentation therapy for patients with OCD who were resistant to standard treatment, usually an SRI (except one study<sup>85</sup> discussed below). All RCTs were placebo-controlled, with parallel groups, except one trial<sup>68</sup> that used a complicated crossover design and involved treatment with risperidone for only two weeks. This trial was excluded from further analysis.

Trials varied in duration from 6 to 16 weeks of therapy. All but one measured a change in the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) as the primary outcome, with “responders” classified as those achieving 25-35 percent improvement on the Y-BOCS scale. In some cases, “responders” were also defined in terms of change in the Clinical Global Improvement (CGI) score. The size of these trials was generally small. The sample sizes ranged from 16 to 44. Quality was measured on the Jadad scale and ranged from 1-4, with nine of the 11 included RCTs scoring 3 or greater.

Nine RCTs were sufficiently clinically similar to justify meta-analysis.<sup>69, 71, 84, 86, 87, 89-92</sup>

The salient features of these RCTs are presented in Table 4. These nine trials were pooled on the outcome “responders,” defined above, measured at 6-16 weeks of therapy (Figure 2). The random effects pooled estimate was an improvement in the relative risk of “responding” of 2.66 (95 percent CI 1.75 - 4.03). This means the number need to treat is 3.6 (2.6, 5.7). The overall score for heterogeneity was significant ( $p=0.036$ ), and the  $I^2$  statistic was 51.6 percent. Only quetiapine and risperidone were included in a sufficient number of studies to permit calculation of pooled estimates for individual drugs, and in both cases, the pooled estimate yielded a statistically significant effect favoring treatment. Relative risk of “responding” was 2.74 (95 percent CI 1.50 – 5.01) for quetiapine and 5.45 (95 percent CI 1.73 – 17.20) for risperidone. The numbers needed to treat are 3.1 (2.0, 6.5) and 2.0 (0.3, 3.3) respectively. Consequently, the evidence of benefit is stronger for quetiapine and risperidone than for olanzapine.

As eight of the nine trials included in the meta-analysis had a Jadad score of 3 or greater, a sensitivity analysis of only the “high quality” trials yielded a result nearly identical to the main result. The Begg's test was not significant ( $p=0.276$ ), but the Eggar's test was significant ( $p=0.02$ ), indicating the presence of unexplained heterogeneity, one explanation for which could be publication bias. However, in some situations, the Eggar's test is considered to be overly sensitive.<sup>93</sup> The grade of evidence for this outcome is considered moderate because of

heterogeneity, and further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Two RCTs of atypical antipsychotics could not be included in our pooled analyses.<sup>85, 88</sup> The first study, presented only in abstract form,<sup>88</sup> assessed the effect of risperidone in 16 patients with SRI-resistant OCD using the CGI score and metabolic changes in the brain as measured by positron emission tomography. Risperidone use was associated with “significant increases” in relative metabolic rate in the striatum, cingulate gyrus, and prefrontal cortex. Four of nine risperidone-treated patients and zero of six placebo-treated patients showed “clinical improvement,” defined as a CGI score of 1 or 2 after 8 weeks of therapy. The second study<sup>85</sup> reported that augmentation therapy with risperidone was more likely to be successful in OCD patients with “bad” scores on the Iowa Gambling Task than in OCD patients with “good” scores. Not all patients in this study were resistant to SRI therapy.

A review article on the use of antipsychotic treatment for OCD was published after we concluded our analysis.<sup>94</sup> This narrative review included eight trials of atypical antipsychotics, which we included in our review, and concluded that the data are promising and support the use of atypical antipsychotics “such as risperidone and quetiapine as a first-line strategy for augmentation in resistant OCD.” Additionally, three meta-analyses have recently been published. The first assessed double blind RCTs, identified nearly the same studies and reached similar conclusions.<sup>95</sup> They concluded that there was strong evidence for both risperidone and haloperidol (a medication outside the scope of our review), and efficacy for olanzapine and quetiapine was not proven. The second meta-analysis included RCTs of antipsychotic drugs as augmentation therapy for serotonergic-resistant obsessive compulsive disorder.<sup>96</sup> The author identified the same 9 RCTs of atypical antipsychotics that we did, plus one additional RCT of augmentation with haloperidol. The authors reported a pooled estimate of responding of 3.31 (95 percent CI 1.40 – 7.84) for augmentation treatment with an antipsychotic. The third meta-analysis concerned just three RCTs of quetiapine augmentation, a subset of the studies used in the other meta-analyses. The study reported a statistically significant benefit for treatment with quetiapine.<sup>97</sup>

## Summary

In summary, a moderate amount of evidence suggests that atypical antipsychotic medications have clinically important effects when used as augmentation therapy for 8 to 16 weeks for patients with OCD resistant to standard treatment. Only risperidone, olanzapine, and quetiapine have been studied. The evidence for benefit of risperidone and quetiapine is stronger than for olanzapine.

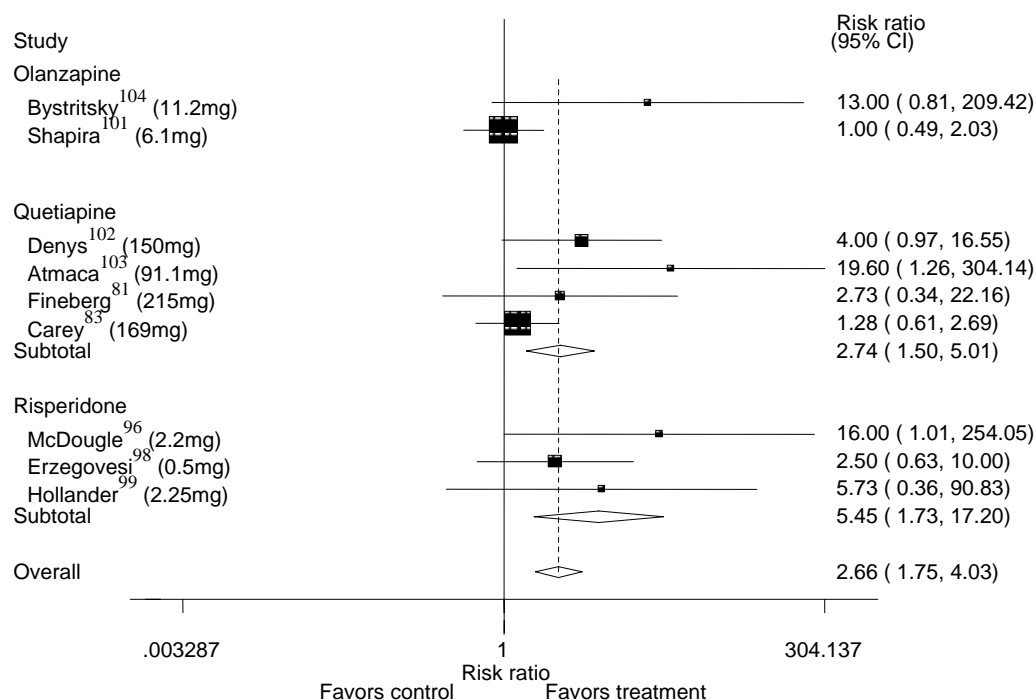
**Table 4. Placebo-controlled trials of atypical antipsychotics as augmentation for obsessive compulsive disorder.**

| Author, Year<br>Jadad Score                 | Subjects   | N  | Treatment                                     | Primary Outcome  | Duration |
|---|--|----|---|--|----------|
| Erzegovesi, 2005 <sup>86</sup><br>Jadad = 4 | Fluvoxamine-refractory OCD patients (non-responders to 12 weeks of therapy)  | 20 | Risperidone 0.5mg                             | Y-BOCS decrease of 35% or greater + CGI                | 6 weeks  |
| Hollander, 2003 <sup>87</sup><br>Jadad = 4  | "Treatment-resistant" OCD: having failed at least 2 trials of SRI therapy. Required to be taking SRI for at least 12 weeks   | 16 | Risperidone (average dose 2.25mg/day)         | Y-BOCS decrease of 25% or greater + CGI                | 8 weeks  |
| Bystritsky, 2004 <sup>92</sup><br>Jadad = 3 | "Refractory" OCD: having no improvement in at least 2 trials of SRI and at least 1 trial of behavioral therapy. Subjects had to be taking fluoxetine, paroxetine, or sertraline for at least 12 weeks. | 26 | Olanzapine (mean dose = 11-2mg/day)           | Y-BOCS decrease of 25% or greater                      | 6 weeks  |
| Atmaca, 2002 <sup>91</sup><br>Jadad = 2     | "Treatment-resistant" OCD: at least one adequate SRI trial before a 3-month open-label trial of SRI; non-responders were selected.   | 27 | Quetiapine (average dose = 91 mg /day)        | Y-BOCS decrease of 30% or greater                      | 8 weeks  |
| Denys, 2004 <sup>90</sup><br>Jadad = 4      | "Refractory" OCD: failure on at least 2 treatments of SRI; all patients were currently taking SRI.   | 20 | Quetiapine titration from 50 mg to 300 mg/day | Y-BOCS decrease of 35% or greater + CGI                | 8 weeks  |
| Shapira, 2004 <sup>89</sup><br>Jadad = 3    | "Fluoxetine-refractory" OCD: 8-week trial of Fluoxetine, non-responders or partial responders were selected.   | 44 | Olanzapine 5mg to 10 mg/day                   | Y-BOCS decrease of 25% or greater                      | 8 weeks  |
| McDougale, 2000 <sup>84</sup><br>Jadad = 4  | "Serotonin inhibitor-refractory" OCD, 12-week open-label SRI monotherapy, refractory patients were selected.   | 36 | Risperidone (average dose = 2.2mg/day)        | Y-BOCS 35% or greater and final score 16 or less + CGI | 6 weeks  |
| Fineberg, 2005 <sup>69</sup><br>Jadad = 3   | "Treatment-Resistant" OCD: at least 12 weeks of SRI treatment at maximum tolerated dose  | 21 | Quetiapine (average dose = 215 mg/day)        | Y-BOCS decrease of 25% or greater                      | 16 weeks |
| Carey, 2005 <sup>71</sup><br>Jadad = 4      | OCD "Failure to respond adequately" to 12 week trials of SRI   | 42 | Quetiapine (average dose = 169 mg/day)        | Y-BOCS decrease of 25% or greater + CGI                | 6 weeks  |

Y-BOCS = Yale Brown Obsessive Compulsive Scale

CGI = Clinical Global Impression Scale

**Figure 2. Pooled analysis of the effect of atypical antipsychotic medications versus placebo on “response” in patients with obsessive-compulsive disorder**



$P = 0.036$  (chi-square test);  $I^2 = 51.6\%$

## Posttraumatic Stress Disorder (PTSD)

### Key Points

- We found four risperidone and two olanzapine trials of over six weeks for PTSD.
- There were 3 trials on men with combat-related PTSD; these showed a benefit in sleep quality, depression, anxiety and overall symptoms when risperidone or olanzapine was used as augmentation therapy.
- We found 3 trials of atypical antipsychotics as monotherapy for women with PTSD; the evidence was inclusive regarding efficacy.
- We found no trials of quetiapine, ziprasidone, or aripiprazole.

Our literature search identified seven placebo-controlled trials of atypical antipsychotics for the treatment of PTSD. One RCT was excluded because the duration of the study was only 5 weeks (a minimum of 6 weeks was our threshold)<sup>98</sup>. Three of the remaining six RCTs assessed atypical antipsychotic treatment as augmentation therapy for men with combat-related PTSD; the



other three assessed atypical antipsychotics as monotherapy for patients with mixed or other forms of PTSD; these patients were almost exclusively women. In one trial,<sup>73</sup> women were allowed to enroll if they were on stable doses of one antidepressant and/or one hypnotic. Salient details of the placebo-controlled trials are presented in Table 5. Almost all trials were small, with only one study enrolling more than 21 patients. Four trials assessed risperidone; the other two trials assessed olanzapine. All trials were relatively short in duration, the longest being 16 weeks. In general, trials suggested benefits of atypical antipsychotics when used as augmentation therapy in men with combat-related PTSD. In contrast, results were mixed in the three small studies of atypical antipsychotics as monotherapy in women with mixed/other forms of PTSD.

The quality of evidence for use as augmentation therapy for combat-related PTSD in men is considered low, based on sparseness of data and that further research is likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. The quality of evidence for use as monotherapy in women with PTSD is considered very low, based on sparseness of data, heterogeneity, and that any estimate of effect is very uncertain.

**Table 5. Posttraumatic Stress Disorder**

| AuthorYear,<br>Jadad Score                    | Subjects   | N              | Treatments                                      | Co-Treatments  | Duration | Outcomes   |
|---|--|----------------|---|--|----------|--|
| <b>Combat-Related PTSD</b>                    |  |                |   |  |          |  |
| Stein, 2002 <sup>99</sup><br>Jadad = 3        | Male veterans with chronic military-related PTSD (DSM-IV)  | 19             | Olanzapine (mean dose=15 mg/day) vs. Placebo    | SSRI   | 8 weeks  | Statistically significant reduction in clinician-administered PTSD scale, Pittsburgh sleep quality index, CES-D, increase in weight (13.2 vs. -3.0 pounds) |
| Monnelly, 2003 <sup>100</sup><br>Jadad = 4    | Male combat veterans with DSM-IV criteria for PTSD and scored $\geq 20$ on Cluster D subscale of the Patient Checklist for PTSD-Military Veterans                    | 15             | Risperidone (mean dose=0.57 mg/day) vs. placebo | Antidepressants, SSRIs, anti-anxiety agents  | 6 weeks  | Statistically significant improvement on irritability symptoms, intrusive thoughts, and total scale for Patient Checklist-Military.                        |
| Bartzokis, 2004 <sup>45</sup><br>Jadad = 3    | Male veterans attending a VA residential psychosocial treatment program for PTSD   | 65             | Risperidone (up to 3 mg/day) vs. placebo        | Residential program, antidepressants, other psychotropic medication, anti-anxiety agents | 16 weeks | Statistically significant improvement on HAM-A, PANSS-P, CAPS-D, CAPS-Total. No difference in side effects between groups                                  |
| <b>Other or Mixed PTSD</b>                    |  |                |   |  |          |  |
| Butterfield, 2001 <sup>101</sup><br>Jadad = 3 | Adults 18-70 attending a university psychiatry clinic or VA women's health center with DSM-IV criteria PTSD  | 15<br>(1 male) | Olanzapine (mean peak dose=14.1mg) vs. placebo  | None reported  | 10 weeks | No difference in PTSD outcomes between groups. Weight gain was 11.5 lbs in the olanzapine group compared to 0.9 lbs with placebo.                          |
| Reich, 2004 <sup>73</sup><br>Jadad = 2        | Women with chronic PTSD due to childhood abuse. DSM-III-R criteria were used, with the SCID and CAPS PTSD scale. Patients needed to have a CAPS-1 score of $\geq 50$ | 21             | Risperidone (mean dose=1.41 mg) vs. placebo     | No co-treatment with other antipsychotic or mood stabilizer was allowed                  | 8 weeks  | Significant benefits for risperidone-treated patients in CAPS-2 total score. Significant increases in prolactin in risperidone-treated patients.           |
| Padala, 2005 <sup>72</sup><br>Jadad = 2       | Women with PTSD diagnosed with mini International Neuropsychiatric interview   | 20             | Risperidone (mean dose=2.62 mg) v. placebo      | No co-treatment allowed  | 11 weeks | A significant benefit for risperidone was observed only for some outcome measures with certain kinds of analysis.  |

## Personality Disorders

### Key Points

- Three 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 nine week trial.
- Aripiprazole was more effective than placebo for the treatment of borderline personality in one small eight week trial.
- We found no studies of quetiapine or ziprasidone for personality disorders.

Our literature search identified six RCTs of atypical antipsychotics for the treatment of personality disorders. Five of these trials evaluated patients who met DSM-IV criteria for borderline personality disorder.<sup>70, 102-105</sup> Another RCT assessed risperidone in the treatment of schizotypal personality disorder.<sup>106</sup> Four of the RCTs were placebo-controlled,<sup>102, 103, 105, 106</sup> one study was an active-controlled trial,<sup>104</sup> and one studied the addition of olanzapine to dialectical behavior therapy.<sup>70</sup> Enrollment ranged from 26 to 60 subjects; the duration of trials ranged from eight weeks to 24 weeks. These trials were considered too clinically heterogeneous to justify pooling, hence our summary of the literature is narrative. Study details are presented in Table 6.

The first study assessed the effect of olanzapine versus placebo in 28 women.<sup>103</sup> The mean age was about 26 years, and most had been treated previously with psychotherapy or other psychotropic medications. Patients were randomized to olanzapine or placebo with dosing adjusted according to perceived response and side effects. The mean daily dose of olanzapine at the endpoint evaluation was 5.3 mg. Using random effects regression modeling (in an attempt to control for baseline values), the study found that olanzapine-treated patients had significantly greater improvements than placebo-treated patients in the Symptom Checklist-90 scales for interpersonal sensitivity, anxiety, anger/hostility, and paranoia. However, there were no differences in SCL-90 anxiety scores based on group means. Still, differences were more marked in the first 4 weeks.

The second study<sup>102</sup> also evaluated olanzapine versus placebo in the treatment of borderline personality disorder. In this study, 40 patients were randomized to receive increasing doses of olanzapine or placebo for 12 weeks. Twenty-three patients had at least one prior suicide attempt, and nine patients had a history of psychiatric hospitalization. Almost two-thirds of patients had a history of non-suicidal self-injurious behavior. The primary outcome was the total score for the nine DSM-IV borderline personality disorder criteria, each scored on a 1-7 Likert scale; the authors called this the *Clinical Global Impressions scale modified for borderline personality*

*disorder*. Using analysis of covariance, the study found statistically significant benefits for olanzapine treatment. Our calculation of standardized mean difference of change in CGI-BPD approached statistical significance. The effect was more pronounced in the first few weeks.

The third olanzapine trial<sup>104</sup> assessed the effect of olanzapine, fluoxetine, or the combination of olanzapine and fluoxetine in women. Forty-five women were randomized to either 10 mg fluoxetine or 2.5 mg of olanzapine or their combination, with the dose subsequently adjusted by an unblinded psychiatrist, according to perceived response and side effects. Subjects and raters were blinded to study assignment. The mean fluoxetine dose at eight weeks for subjects treated only with fluoxetine was 15 mg; and the mean dose of olanzapine for olanzapine-treated subjects was 3.3 mg. In comparison, for the combination group, the mean dose of fluoxetine was 13 mg and that of olanzapine was 3.2 mg. Using random effects regression modeling, the study reported improvements in the modified overt aggression scale and the Montgomery-Asberg depression rating for patients. In general, symptomatically, patients on the combination of olanzapine and fluoxetine resembled those treated with olanzapine alone.

The fourth BPD trial assessed the effects of adding olanzapine to dialectical therapy on 60 patients.<sup>70</sup> All patients received dialectical therapy and were randomized to receive placebo or olanzapine at a flexible dose of 5 to 20 mg/day for 12 weeks. Almost 90 percent of enrolled subjects were women. Patients treated with olanzapine experienced a significant (two-point) improvement in the Hamilton Depression Score and a decrease in impulsive behavior compared with those on placebo.

Completion rates in the olanzapine trials ranged from about 50 percent to 93 percent. Mean weight gain in the olanzapine groups ranged from 1.29 to 8.9 kg; weight gain was always significantly higher than in the comparator groups. Mild sedation was common among olanzapine patients. No serious movement disorders were reported in any of the olanzapine groups.

The fifth trial assessed the effect of risperidone for the treatment of schizotypal personality disorder.<sup>106</sup> Twenty-five subjects with DSM-IV criteria for schizotypal personality disorder who did not meet current or lifetime DSM-IV criteria for schizophrenia or any schizophrenia-related psychiatric disorder or bipolar disorder were randomized after a single-blind, two-week, placebo lead-in period to either risperidone (titrated upward in a stepwise fashion) or placebo and then followed for 9 weeks. Most of the enrolled subjects were men, and the mean age was about 40. Most had comorbid personality disorders, usually paranoid, narcissistic, or avoidant. About 60 percent of subjects completed the trial. Risperidone-treated subjects experienced greater improvement on the Positive And Negative Syndrome Scale (PANSS) than did placebo controls. The risperidone group also had greater improvements on the Clinical Global Impression scale, the Hamilton Rating Scale for Depression, and the Schizotypal personality questionnaire than did the placebo group, but these improvements did not reach statistical significance. Side effects were reported by about half of the patients in each group. The authors concluded that low-dose risperidone appeared to be effective in reducing symptom severity in schizotypal personality disorder and was generally well tolerated.

The sixth trial assessed the effect of aripiprazole for the treatment of borderline personality disorder.<sup>105</sup> Fifty seven subjects (more than 80 percent female, mean age = 22) with DSM-IV criteria for borderline personality disorder were randomized to aripiprazole 15 mg/day or placebo. Subjects were followed for 8 weeks using the Symptom Checklist (SCL-90-R), the Hamilton Rating Scales for both Depression and Anxiety (HAM-D, HAM-A), and the State-Trait Anger Expression Inventory. Five subjects were withdrawn (groups not specified). On the SCL-

90-R and HAM-D subjects reported much greater reductions in depression, while reductions in anxiety on the HAM-A were more modest but still statistically significant. SCL-90-R domains that improved with aripiprazole more than placebo were obsessive-compulsive, insecurity in social contacts, aggressiveness/hostility, phobic thinking, paranoid thinking and psychoticism.

## **Summary**

The modest size of the effect on most outcomes, the small size of the trials, the dropouts or loss to follow-up (in the majority of trials being 40 percent or greater), and the way the outcomes and statistical analyses were presented limit the ability to draw firm conclusions. The strength of evidence for all outcomes in this condition is very low due to sparseness of data and very serious limitations about study quality, with the result that any estimate of effect is very uncertain.

**Table 6. Personality Disorders**

| Author, Year, Jadad score | Subject (s)   | N  | Treatment   | Duration | Outcomes   |
|---------------------------|---|----|---|----------|--|
| Soler, 2005, 2            | Borderline Personality Disorder, 90% women              | 60 | Dialectical therapy + Placebo vs. dialectical therapy + Olanzapine, flexible dose | 12 weeks | Change in HAM-D favoring Olanzapine SMD = 2.438 (1.765, 3.111); Change in CGI-S favoring Olanzapine WMD = -11.87(-14.226, -9.514)                                  |
| Bogenschultz, 2004, 3     | Borderline Personality Disorder, Age 18 to 54, 38% male | 40 | Placebo vs. Olanzapine Adjustable dosing  | 12 weeks | Change in CGI-BPD SMD = -.667 (-1.351, 0.018) No differences in SCL-90 scales.   |
| Zanarini, 2001, 5         | Borderline Personality Disorder, Females ages 18-40     | 28 | Placebo vs. Olanzapine Adjustable dosing  | 24 weeks | Final change in SCL-90 anxiety disorder not significant between groups. Olanzapine group experienced faster rate of change in anxiety, paranoia, anger/ hostility. |
| Zanarini, 2004, 2         | Borderline Personality Disorder, Females 18-40          | 45 | Fluoxetine vs. Olanzapine vs. Olanzapine + Fluoxetine                             | 8 weeks  | Change in MADRAS not significant between groups.   |
| Nichels, 2006, 4          | Borderline Personality Disorder, 17% male, Age >=16     | 52 | Placebo vs. Aripiprazole, 15mg fixed dose   | 8 weeks  | Change in HAM-D, HAM-A, STAEI, and most of SCL-90 scales favoring aripiprazole   |
| Koenigsberg, 2003, 4      | Schizotypal Personality Disorder, Age 18-60, 83% male   | 25 | Placebo vs. Risperidone, up to 2 mg/day   | 9 weeks  | Change in PANSS-TOTAL favoring risperidone - 1.624 (-2.595 to -0.653)  |

SMD = Standardized Mean Difference, WMD = Weighted Mean Difference

PANSS = Positive And Negative Syndrome Scale

MADRAS = Montgomery-Asberg Depression Rating Scale

HAM-D = Hamilton Depression Scale

SCL-90 = Symptom Checklist 90

CGI = Clinical Global Impression Scale

# Tourette's Syndrome

## Key Points

- We found four trials of risperidone and one of ziprasidone for this condition.
- The little evidence available is inconclusive about the efficacy of either drug.
- We found no studies of aripiprazole, quetiapine, or olanzapine for Tourette's symptoms.

Our literature search identified five RCTs testing the effects of atypical antipsychotics in the treatment of children and adolescents with Tourette's syndrome.<sup>107-111</sup> Enrollment ranged from 19 to 51 subjects; length ranged from eight to 12 weeks. One RCT compared ziprasidone with placebo, another RCT compared risperidone with placebo,<sup>108</sup> and the other three RCTs compared risperidone with either pimozide or clonidine. Trial data is displayed in Table 7.

The first RCT was an 8-week placebo-controlled trial of ziprasidone in 28 patients, mostly male, ages 7-17 years (mean age 11).<sup>107</sup> Patients were randomized to receive either ziprasidone (starting at 5 mg and adjusted as tolerated to a maximum total daily dose of 40 mg, given as 20 mg twice daily) or placebo. Twenty-four patients completed the study. At 8 weeks, patients in the ziprasidone group experienced significant reductions when adjusted for pre-treatment values in the YGTSS Global Severity scores (decrease of 39 percent versus 16.2 percent,  $p=0.016$ ) and total tic scores (decrease of 34.8 percent versus 6.9 percent,  $p=0.008$ ). However, between group means were not significantly different. No significant differences were seen between groups in the Clinical Global Impression Severity scale scores. All 16 patients in the ziprasidone group and just over half of the patients in the placebo group experienced a "treatment-emergent" adverse event.

The second placebo-controlled trial assessed 34 patients, of whom 26 were children.<sup>108</sup> These patients were randomized to receive either risperidone at a titrated dose not to exceed 3 mg/day or placebo. After 8 weeks, the risperidone treated children experienced a significant reduction in YGTSS Total Tic scores (36 percent v. 9 percent reduction). Nine of 12 children treated with risperidone (compared with one of 14 treated with placebo) were deemed responders on the Clinical Global Impressions-Improvement measure.

The third trial compared risperidone with pimozide.<sup>109</sup> Patients up to age 50 were enrolled, however the median age was in the early 20s. Obsessive-compulsive symptoms were present in about half of patients in addition to Tourette's symptoms. Patients were randomized to receive either a fixed dose titration for the first week followed by flexible dosing for a period of 7 weeks or placebo treatment. The risperidone dose varied from 0.5-2.0 mg per day, and the pimozide dose varied from 1-2 mg per day. At the end of the study, both groups experienced significant improvements in the Tourette's syndrome severity scale and the Clinical Global Impressions scale, and there were improvements on most of the secondary outcomes, including the Hamilton rating scale for anxiety and the Yale-Brown Obsessive Compulsive Scale. However, there were no differences between groups in any of these outcomes. The authors report that younger patients in both groups had consistently better scores at baseline and at the endpoint but that overall age had little effect on the efficacy of either pimozide or risperidone.

The fourth RCT compared the effects of risperidone (mean dose 2.5 mg/day) with those of pimozide (mean dose 2.4 mg/day) in an 8 week crossover trial in 19 children with Tourette's or

chronic motor tic disorder (as defined in the DSM-IV-TR).<sup>110</sup> The dropout rate was approximately 33 percent. The YGTSS score was significantly lower during risperidone treatment than during pimozide treatment (42 percent decrease v. 16 percent decrease). No significant differences were found in Clinical Global Impression-Severity outcomes.

The fifth trial compared risperidone to clonidine in a RCT of 21 children and adolescents (90 percent male; average age 11).<sup>111</sup> Patients were randomized after completing a 7-14 day, single-blind, placebo lead-in to titrated doses of either risperidone or clonidine. The mean dose of risperidone at the end of the 8-week study was 1.5 mg per day, while the mean dose of clonidine was 0.175 mg per day. For the main outcome measures, which included the YGTSS, the Yale-Brown Obsessive Compulsive Scale, and the DuPaul Attention Deficit Hyperactivity Scale, both groups experienced significant improvements over time, but no significant differences were found between the drugs.

Mean weight gain in the risperidone groups ranged from 2.1 kg to 3.9 kg per study; this was always more than the comparator groups. Weight gain with ziprasidone was similar to placebo. Transient mild sedation was common with ziprasidone. In addition, five boys in the ziprasidone group experienced above normal serum prolactin levels. Risperidone was well tolerated in the studies; adverse events included fatigue, somnolence, sedation, and stiffness.

## **Summary**

Four small trials of risperidone provide evidence that it is more effective than placebo, and at least as effective as pimozide and clonidine, in children and adolescents with Tourette's syndrome for 8 to 12 weeks of therapy. Risperidone caused significant weight gain in these studies. The one available study of ziprasidone showed variable effectiveness compared to placebo. The strength of evidence for risperidone is low based on very sparse data and that future research is very likely to have an important effect on our confidence in the estimate of effect. For ziprasidone, the strength of evidence is very low based on sparseness and heterogeneity, and any estimate of effect is very uncertain.



**Table 7. Tourette's Syndrome**

| <b>Author, Year, Jadad score</b> | <b>Subjects</b>   | <b>N</b>         | <b>Treatment</b>   | <b>Duration</b>            | <b>Outcomes</b>   |
|----------------------------------|---|------------------|--|----------------------------|---|
| Sallee, 2000, 3                  | Age 7 to 17, 79% male, severe tic symptoms, free of psychotropic meds 4 weeks | 28               | Ziprasidone 5 to 40 mg/day vs. Placebo                   | 8 weeks                    | Ziprasidone group had significant reductions in Yale Global Tic Severity Scale compared to placebo. Differences in change in CGI-S not significant. |
| Scahill, 2003, 3                 | Age 6 to 62, 88% male   | 34 (26 children) | Risperidone vs. Placebo<br>Adjustable dosing             | 8 weeks                    | Change in Yale Global Tic Severity Scale favors risperidone SMD = -1.090 (-1.814, -0.365), Also, more "responders" on CGI-I.                        |
| Bruggerman, 2001, 5              | Age 11 to 50, 88% male, 50% OCD symptoms                                      | 51               | Pimozide vs. Risperidone, Flexible dosing                | 12 weeks                   | No significant differences between pimozide and risperidone in change in CGI, TSSS.   |
| Gilbert, 2004, 5                 | Age 7 to 17, 79% male, severe tic symptoms                                    | 19               | Crossover<br>Pimozide vs. Risperidone, Adjustable dosing | 12 weeks, cross at 4 weeks | Change in Yale Global Tic Severity Scale greater in risperidone at 4 weeks  |
| Gaffney, 2002, 3                 | Age 7 to 17, 90% male   | 21               | Clonidine vs. Risperidone, Adjustable dosing             | 8 weeks                    | No significant differences between clonidine and risperidone in change in Yale Global Tic Severity Scale, CGI.                                      |

TSSS = Tourette's Syndrome Severity Score

CGI = Clinical Global Impression Scale

# Autism

## Key Points

- In October 2006, the FDA approved the use of risperidone for autism.
- Two trials of eight weeks duration support the superiority of risperidone over placebo in improving serious behavioral problems in children with autism.
- We found no trials of olanzapine, quetiapine, ziprasidone or aripiprazole for this indication.

Our literature search identified reports of one open-label pilot study<sup>112</sup> and two placebo-controlled trials<sup>113, 114</sup> and one abstract<sup>115</sup> that reported on a subgroup analysis of one of the placebo-controlled trials<sup>113</sup> assessing use of atypical antipsychotics medications for children with autism.

The pilot study enrolled 12 children with the DSM-IV diagnosis of autistic disorder and randomized them to 6 weeks of open treatment with olanzapine or haloperidol;<sup>112</sup> it and was not included in our analyses due to small sample size.

The first placebo-controlled trial assessed the effect of risperidone in the treatment of children (81 boys and 20 girls; mean age approximately 9 years) who met DSM-IV criteria for autistic disorder.<sup>113</sup> Subjects were given increasing doses of risperidone to a maximum of 2.5 mg per day (mean 1.8 mg during the final week) and followed for 8 weeks. The primary outcome measure was the irritability subscale of the Aberrant Behavior Checklist. The study found improvement over time in both placebo- and risperidone-treated groups, with a significantly greater effect for risperidone than placebo (57 percent decrease versus 14 percent decrease, respectively;  $p < 0.001$ ). With a “positive response” defined as a 25 percent improvement in the score on the irritability subscale and a rating of “much improved” or “very much improved” on the Clinical Global Impressions-Improvement Scale, 69 percent percent of risperidone-treated children were considered to have a “positive response” compared to 12 percent of placebo-treated children ( $p < 0.001$ ). In a 6-month open-label extension, about two-thirds of patients who had a positive response in the double-blind phase of the study maintained these improvements. Improvements were seen in several secondary outcome measures as well. A greater mean increase in weight was seen in the risperidone group (2.7 kg) than in the placebo group (0.8 kg) ( $p < 0.001$ ). However, no serious adverse events were found in the risperidone-treated group, and no child was withdrawn from the study because of an adverse event. The most common adverse events, in addition to increased appetite and weight gain, were drowsiness, fatigue, and nasal congestion. No extrapyramidal symptoms were observed in either group. The authors concluded that risperidone was safe and effective for the short-term treatment of tantrums, aggression, and self-injurious behavior in children with autistic disorder. In a subsequent paper, the same group of authors reported that risperidone was superior to placebo in reducing symptoms of most concern to the parents of these autistic children.<sup>116</sup>

The second placebo-controlled trial assessed the use of risperidone in 79 children (ages 5-12; average age 7 to 8; approximately 75 percent were male) who had a DSM-IV diagnosis of pervasive developmental disorder and a total score of 30 or more on the Childhood Autism Rating Scale.<sup>114</sup> About 70 percent of patients had a diagnosis of autistic disorder, with the

remainder having Asperger's disorder or other pervasive developmental disorders. Patients were randomized to a titrated dose of risperidone or placebo and followed for 8 weeks (final dose 1.5 mg/day). Both groups improved on the irritability subscale of the Aberrant Behavior Checklist, but the risperidone-treated children improved significantly more than the placebo group (64 percent versus 31 percent, respectively). As in the previous study, several secondary outcome measures also improved. The most common side effects reported for risperidone-treated children were somnolence, upper-respiratory tract infection, rhinitis, and increased appetite. The authors concluded that risperidone was effective for relieving many of the behavioral symptoms associated with pervasive developmental disorder in children.

## **Summary**

Two placebo-controlled trials of moderate size and eight weeks duration reported consistent evidence that risperidone is superior to placebo in improving serious behavioral problems in children with autism. The quality of evidence for outcomes in this condition is considered low due to the sparseness of data, and that further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

## **Sensitivity Analysis**

We conducted a sensitivity analysis on study quality. We extracted outcome data on 60 trials. Studies of better quality (as defined by scores of 3 or more on the Jadad scale) reported a 25 percent lower effect size than studies of lower quality, a result that was of borderline statistical significance ( $p=0.058$ ).

The funding for 53 of the 60 trials for which we extracted outcome data (88 percent) was provided at least partly by the pharmaceutical industry, which precluded any assessment of differential effects associated with funding source. However, a recent relevant review of the relationship between industry sponsorship and the results of head-to-head trials of atypical antipsychotics (for all conditions) found that in 90 percent of such trials, the sponsor's drug was reported to be superior to the comparison.<sup>93</sup> This finding led to apparently contradictory conclusions about the superiority of one atypical antipsychotic over another, depending on the sponsorship of the trial. We presume this bias is also present for trials that compare a sponsor's drug to placebo. Therefore, the results of manufacturer-sponsored trials should be interpreted with caution.

We planned sensitivity analyses on dose and duration of treatment. However, these variables are condition-specific (and drug-specific in terms of dose) and too few trials were available within any one condition to support an analysis.

## **Publication Bias**

The presence of possible publication bias was detected using the Begg's test and Eggar's test on the set of 60 studies for which we extracted effect sizes. Both tests yielded statistically significant results ( $p=0.001$  or less). This finding indicates the presence of unexplained heterogeneity in trials. One possible source of heterogeneity is publication bias. Another potential explanation is that all the drugs do not work equally well for all conditions. It is not possible for us to more precisely determine the source of the heterogeneity. When assessed by

condition, only OCD yielded statistically significant test results (as reported previously and then in only one of two tests). However, the lack of statistical significance for either test cannot be construed to mean that publication bias does not exist. We assume that publication bias may be present for all conditions, resulting in an overestimation of the potential efficacy of these drugs for all conditions.

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

#### **Key Point**

There was insufficient information to answer this question. Therefore, it is included as a topic for future research.

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

#### **Key Points**

- 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 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 versus 2.3 percent of patients randomized to receive placebo. The odds ratio for death was 1.54, with a 95 percent confidence interval 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 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 (OR 3.88, 95 percent CI 1.49 to 11.91). This risk was equivalent to one additional stroke for every 31 patients treated in this patient population, i.e., number needed to harm (NNH) 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 than 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 three risperidone trials which 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.
- 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 the others groups (5 percent vs. 0-1 percent).
- Ziprasidone was associated with an increase in EPS when compared to placebo in a pooled analysis of adults with depression, or PTSD, or personality disorders (OR 3.32 95 percent CI 1.12 to 13.41).
- 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.

## Detailed Analyses

One of the major rationales for preferring treatment with atypical antipsychotics over conventional antipsychotics is potentially greater safety. We examined adverse event data from all RCTs of atypical antipsychotics for off-label conditions, plus cohort studies and cases series with more than 1,000 subjects. To analyze the data from RCTs, we further divided them into

placebo-controlled trials, active-controlled trials, and head-to-head comparisons of atypical antipsychotics. We also discuss a recent meta-analysis of deaths in patients with dementia who were treated with atypical antipsychotics. A similar analysis led the FDA to issue a Public Health Advisory for treatment of dementia with atypical antipsychotics in 2005.

Of the 131 reports on RCTs, 119 reported adverse events. We excluded articles that reported data from a study already in the analysis (n= 26). Twenty trials did not report the appropriate count data, three did not report the data by treatment group, and three did not report on a comparison of interest. Thus, we extracted adverse event data from 67 RCTs. We also found 15 observational studies (case series and cohort) of more than 1,000 subjects. Five observational studies did not report the appropriate count data, three did not report the data by treatment group, and one did not report on a comparison of interest. Thus, we were able to include six observational studies in our adverse events analyses.

We identified and grouped the reports of adverse events into clinically relevant categories. These categories were then pooled within three condition categories, based on patient age. Patient age was a proxy measure for the baseline likelihood of adverse events; in other words, children, adults, and the very old are expected to have potentially different types of risks for adverse events. We analyzed studies of dementia patients separately (mean age = 80); pooled across the conditions of depression, obsessive-compulsive disorder, personality disorder, and PTSD (mean ages between 31 years and 46 years by conditions); and pooled across the conditions of autism (mean age = 7.8) and Tourette's (mean age = 18.2). We did not pool across drugs; instead we generated separate estimates for each of the five atypical antipsychotics. Separate analyses were conducted for placebo comparisons, active comparisons (comparing atypical antipsychotics to acetylcholinesterase inhibitors, benzodiazepines, clonidine, conventional antipsychotics, mood-stabilizers, SRIs, and tricyclic antidepressants), and the few head-to-head trials of atypical antipsychotics. We also analyzed a few studies that compared an atypical added to a conventional therapy (for example, studies of an SRI versus an SRI plus an atypical antipsychotic).

The complete results of the adverse event analyses are presented in Appendix E. Number needed to harm (NNH) is presented where applicable. For many of the comparisons, the numbers of RCTs and observational studies are few and the number of enrolled patients is small, resulting in wide 95 percent confidence intervals and the inability to draw conclusions. However, even with this limitation, many observations are worth noting.

## **Dementia**

Our adverse events analyses for dementia included 13 placebo-controlled trials, six active-controlled trials, five head-to-head trials, and three observational studies.

In the placebo-controlled trials (PCTs), olanzapine was statistically associated with increases in appetite/weight (OR 6.12, 95 percent CI: 1.49 to 54.04, NNH = 19), as well as anticholinergic events (OR 3.29, 95 percent CI: 1.62 to 7.17, NNH = 5). In the CATIE trial, 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.

The group of symptoms which we categorized as cardiovascular (including "cardiovascular symptoms," "edema," and "vasodilation") was reported significantly more often in patients taking olanzapine or risperidone than in those taking placebo (OR of 3.31 and 2.33 respectively).

The number needed to harm was 25 for olanzapine and 16 for risperidone. Cerebrovascular accident (CVA) was reported in three placebo-controlled trials of risperidone; the drug was associated with an increase in CVA. Number needed to harm was 31. Aripiprazole and olanzapine were not associated with an increase in CVA in the trials of each where CVA was reported. No trials of quetiapine or ziprasidone reported CVA. Table 8 displays our analyses.

**Table 8. Cardiovascular adverse events among dementia patients – Atypical Antipsychotics Compared to Placebo**

| Adverse Events         | Drug        | # of studies | Placebo          |             | Intervention Groups |             | Pooled OR | 95% CI        | NNH | 95% CI NNH |
|------------------------|-------------|--------------|------------------|-------------|---------------------|-------------|-----------|---------------|-----|------------|
|                        |             |              | # adverse events | sample size | # adverse events    | sample size |           |               |     |            |
| Cardiovascular/CVA     | Olanzapine  | 2            | 2                | 232         | 5                   | 278         | 2.09      | (0.32, 23.27) | NC  | NC         |
| Cardiovascular/CVA     | Risperidone | 3            | 6                | 550         | 21                  | 487         | 3.88      | (1.49, 11.91) | 31  | (19, 82)   |
| Cardiovascular – other | Olanzapine  | 4            | 5                | 298         | 38                  | 678         | 3.31      | (1.27, 10.91) | 25  | (16, 60)   |
| Cardiovascular – other | Risperidone | 4            | 27               | 665         | 110                 | 1060        | 2.33      | (1.48, 3.78)  | 16  | (12, 25)   |

NC = Not calculated

To analyze extrapyramidal side effects (EPS), we were able to pool three PCTs for aripiprazole and four PCTs for risperidone. Both drugs were associated with an increase in EPS (OR 2.53 and 2.82 respectively) compared to placebo. The NNH for aripiprazole was 16, for risperidone 13. There was insufficient EPS data to pool for olanzapine, quetiapine, and ziprasidone.

Risperidone, olanzapine and aripiprazole were each associated with sedation in dementia PCTs. The NNH ranged from eight to ten. Table 9, below, displays analyses on neurological side effects.

**Table 9. Neurological adverse events among dementia patients – Atypical Antipsychotics Compared to Placebo**

| Adverse Events                             | Drug         | # of studies | Placebo          |             | Intervention Groups |             | Pooled OR | 95% CI       | NNH | 95% CI NNH |
|--|--------------|--------------|------------------|-------------|---------------------|-------------|-----------|--------------|-----|------------|
|  |              |              | # adverse events | sample size | # adverse events    | sample size |           |              |     |            |
| Neuro/Movement Disorder/EPS                | Aripiprazole | 3            | 16               | 348         | 39                  | 359         | 2.53      | (1.34, 5.01) | 16  | (10, 42)   |
| Neuro/Movement Disorder/EPS                | Risperidone  | 4            | 29               | 713         | 114                 | 949         | 2.82      | (1.81, 4.51) | 13  | (10, 18)   |
| Neuro/Movement Disorder/Gait               | Olanzapine   | 4            | 15               | 373         | 79                  | 641         | 2.75      | (1.52, 5.79) | 12  | (9, 20)    |
| Neuro/Movement Disorder/Gait               | Risperidone  | 3            | 8                | 406         | 32                  | 448         | 3.04      | (1.32, 7.84) | 19  | (13, 41)   |
| Neuro/Movement Disorder/Tardive Dyskinesia | Risperidone  | 3            | 14               | 475         | 4                   | 714         | 0.31      | (0.07, 1.03) | NC  | NC         |

|                |              |   |    |     |     |      |      |               |    |         |
|----------------|--------------|---|----|-----|-----|------|------|---------------|----|---------|
| Neuro/Sedation | Aripiprazole | 3 | 10 | 348 | 54  | 359  | 6.68 | (3.19, 15.72) | 8  | (6, 12) |
| Neuro/Sedation | Olanzapine   | 5 | 24 | 440 | 152 | 778  | 4.26 | (2.66, 7.08)  | 8  | (6, 12) |
| Neuro/Sedation | Risperidone  | 6 | 87 | 922 | 249 | 1260 | 2.50 | (1.89, 3.34)  | 10 | (8, 13) |

NC = Not Calculated

Olanzapine, risperidone, and aripiprazole were each associated with a significant increase in the constellation of symptoms we categorize as other neurological (including “confusion,” “dizziness,” “dizziness and headaches,” “lightheadedness,” “orthostatic dizziness,” “seizure,” and “tinnitus”). Aripiprazole, olanzapine, and risperidone were associated with an increase in fatigue (OR of 3.67, 2.37, and 3.56, respectively). The latter two drugs were also associated with gait disorders in dementia patients.

Urinary symptoms were significantly more common in dementia patients treated with aripiprazole and risperidone than with placebo (OR of 4.07 and 1.55 respectively). There was insufficient data to conduct analysis for ziprasidone or quetiapine.

**Table 10. Urinary adverse events among dementia patients – Atypical Antipsychotics Compared to Placebo**

| Adverse Events | Drug         | # of studies | Placebo          |             | Intervention Groups |             | Pooled OR | 95% CI       | NNH | 95% CI NNH |
|----------------|--------------|--------------|------------------|-------------|---------------------|-------------|-----------|--------------|-----|------------|
|                |              |              | # adverse events | sample size | # adverse events    | sample size |           |              |     |            |
| Urinary        | Aripiprazole | 3            | 45               | 348         | 115                 | 359         | 4.07      | (2.61, 6.44) | 5   | (4, 8)     |
| Urinary        | Risperidone  | 4            | 71               | 665         | 164                 | 1060        | 1.55      | (1.13, 2.13) | 21  | (13, 63)   |

In a trial of risperidone versus acetylcholinesterase inhibitors in 27 dementia subjects, risperidone patients had significantly fewer gastro-intestinal events. A trial of olanzapine versus benzodiazepines in 205 patients showed no significant difference in adverse events.

In a very small trial of risperidone and olanzapine versus conventional antipsychotics (n = 40), no patients on atypicals reported decreased salivation, compared to six subjects on conventional antipsychotics. Fewer olanzapine subjects reported blood pressure decrease and cardiovascular rhythm irregularities in this trial.

Adverse events were analyzed in one trial that compared risperidone plus rivastigmine to rivastigmine alone. While several events were noted in these dementia patients, the risks did not differ significantly between treatment groups.

In two head-to-head dementia studies, olanzapine subjects had significantly higher odds of weight gain or increase in appetite (OR 2.98, 95 percent CI:1.08 to 9.50) than risperidone subjects. In one head-to-head trial, a risperidone subject reported a pulmonary adverse event, compared with no subjects in the olanzapine group.

Recently, the Clinical Antipsychotic Trials of Intervention Effectiveness – Alzheimer’s Disease (CATIE-AD) trial was published; 4 compared olanzapine, quetiapine, and risperidone to each other and to placebo.<sup>19</sup> The design of this trial is discussed in more detail earlier. In terms



of adverse events, all three atypical antipsychotics were 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 the others groups (5 percent vs. 0-1 percent). Weight gain was greatest in the olanzapine group (gain of 1.0 pound per month vs. gain of 0.4 - 0.7. pound per month).

Observational studies of dementia patients found that olanzapine patients had lower odds of CVA than quetiapine patients (OR 0.83) or risperidone patients (OR 0.71). However, these results did not meet conventional levels of statistical significance (95 percent CIs: 0.65 to 1.06, 0.45 to 1.11). Risperidone patients had higher odds of CVA than untreated patients (OR 1.35, 95 percent CI: 1.07 TO 1.71).

In two trials of aripiprazole, dermatologic problems were significantly more likely than in patients taking placebo (OR 2.53, 95 percent CI: 1.54 to 3.62, NNH = 6).

### **Meta-Analyses of the Effect of Atypical Antipsychotic use on the Risk of Death and Other Side Effects in Patients with Dementia**

A meta-analysis of atypical antipsychotic medication use and death in Alzheimer's disease patients was recently published.<sup>14</sup> This meta-analysis included both published and unpublished randomized placebo-controlled parallel group clinical trials of atypical antipsychotics. Fifteen RCTs were included (eight were cited only as abstracts): four trials of risperidone, five trials of olanzapine, three trials of quetiapine, and three trials of aripiprazole. In all, 3,353 patients received an atypical antipsychotic, and 1,757 received placebo. With one exception, trials lasted from 6-12 weeks. (The one exception was 26 weeks.) Death occurred in 118 or 3.5 percent of patients randomized to receive atypical antipsychotics versus 40 or 2.3 percent of patients randomized to receive placebo. The odds ratio for death using a fixed effects model was 1.54, with a 95 percent confidence interval of 1.06 to 2.23. The difference in risk for death was small but statistically significant ( $p = .01$ ). In other words, the number needed to harm was 100, although the 95 percent confidence intervals were broad. Pooled data from 2 trials containing a haloperidol treatment arm indicated that treatment with this conventional antipsychotic was also associated with a similar, albeit not statistically significant, increase in death. The authors concluded that atypical antipsychotic drugs may be associated with a small increased risk for death compared with placebo. A very similar analysis performed by the FDA was sufficient for the FDA to issue a 2005 Public Health Advisory regarding the use of atypical antipsychotics in elderly persons with dementia. Other reports attribute the increased risk of death to cerebrovascular events.<sup>117, 118</sup>

These authors also published the effectiveness meta-analysis discussed earlier<sup>13</sup>. They reported that adverse events were inconsistently reported among trials and that most did not report adverse events that occurred less than 5 percent or 10 percent of the time, meaning potentially significant adverse events may have been left out. Somnolence was consistently identified as a statistically significant increased risk, with an odds ratio of 2.84. No effect was seen on accidental injury or falls. Compared with placebo, extrapyramidal effects were more common in risperidone-treated patients but not in patients treated with other atypical antipsychotics. Data from a small number of trials showed an increased risk of abnormal gait. In placebo controlled trials of risperidone and olanzapine, there was increased risk of edema.

Compared with placebo, cardiovascular adverse events were more common in risperidone-treated patients, and in patients treated with atypical antipsychotics overall.

After we completed our analyses, the manufacturers of olanzapine published an analysis comparing that drug to placebo, risperidone, and conventional antipsychotics in elderly patients with dementia.<sup>119</sup> They reviewed six controlled trials and found that the incidence of mortality was significantly higher in olanzapine patients than in those treated with placebo. Differences in mortality between olanzapine and risperidone were not statistically significant; nor were differences between olanzapine and conventional antipsychotics. Incidence of cerebrovascular adverse events (hemorrhagic strokes, ischemic strokes, cerebrovascular accidents, or transient ischemic attacks) was three times higher in olanzapine patients than in the placebo patients; differences between olanzapine and risperidone and olanzapine and conventional antipsychotics were not significant.

As this report was being finalized, three abstracts from AHRQ's Developing Evidence to Inform Decisions about Effectiveness (DEcIDE) program were made available. Each of the studies used health care utilization data for British Columbia adults aged 65 years or older to assess the association between use of conventional antipsychotics, atypical antipsychotics, and death. Users of conventional antipsychotics had a 35 percent increased mortality risk compared to atypical antipsychotics users; this increase was attributable to increased fatal out-of-hospital cardiac events, pneumonia, and stroke.<sup>120-122</sup>

### **Children/Adolescents with Tourette's Syndrome or Autism**

Our adverse events analyses for Tourette's syndrome and autism included four placebo-controlled trials and three active-controlled trials. There were no head-to-head trials or observational studies with usable data for these conditions.

Results showed several statistically significant differences between atypical antipsychotics and placebo. With risperidone, weight gain was 5.94 times more likely (95 percent CI: 2.94 to 12.62, NNH = 4) and decreased blood pressure was 12.47 times more likely than with placebo (NNH = 9). However, the confidence interval for decreased blood pressure was very wide (95 percent CI: 1.75 to 547.58). Odds were 3.24 times higher for gastrointestinal problems (95 percent CI: 1.41 to 7.92) and 5.35 times higher for increased salivation with risperidone. Risperidone subjects also had higher odds than placebo subjects for fatigue (OR 4.40; 95 percent CI: 2.04 to 9.94), extrapyramidal effects (OR 4.85, 95 percent CI: 2.15 to 12.08), and sedation (OR 12.09; CI: 5.40 to 29.61).

The one placebo-controlled trial of ziprasidone had only 28 patients and showed no significant difference in adverse events between groups.

A study comparing risperidone with clonidine had only 17 subjects and showed no significant differences in adverse events between groups. Olanzapine and risperidone were each compared with conventional antipsychotics in one trial; fewer risperidone patients had sleep disorders.

### **Depression, OCD, PTSD, Personality Disorders**

Our adverse events analyses for these conditions included 20 placebo-controlled trials, 13 active-controlled trials, three head-to-head trials, six augmentation trials, and three observational studies.

In the placebo-controlled trials (PCTs), olanzapine was statistically associated with increases in appetite/weight gain (OR 11.16, 95 percent CI: 7.40 to 17.24). In one small PCT of risperidone, three out of 20 subjects in the treatment group reported weight gain, compared with no placebo subjects. In one PCT of ziprasidone, two out of 210 treatment subjects reported weight gain, compared with no placebo subjects.

Regarding cardiovascular symptoms, in one PCT (N = 201) seven olanzapine subjects reported them, compared with no placebo subjects. In a PCT of ziprasidone (N= 139), two treatment subjects reported them, compared to no placebo subjects.

Decreased salivation was significantly more common in subjects taking olanzapine and quetiapine than placebo (ORs 2.71 and 8.90, respectively). In two PCTs, liver function test abnormalities were more common in patients taking olanzapine (12 of 171 treated patients compared to none of 169 placebo patients). In a PCT of ziprasidone, one treatment subject had an abnormal liver function test; no one in the placebo group did.

When compared to placebo, all atypical antipsychotics were associated with an increase in at least some symptoms categorized as neurological (“confusion,” “dizziness,” “headaches,” “lightheadedness,” “orthostatic dizziness,” “seizure,” and “tinnitus”). Specifically, ziprasidone was associated with a significant increase in extrapyramidal side effects (OR 3.32, 95 percent CI: 1.12 to 13.41). All atypicals except aripiprazole were significantly associated with sedation; NNHs ranged from 2 to 6. In three studies that reported on headache, olanzapine subjects had lower odds of headache than placebo subjects (OR 0.69, 95 percent CI: 0.48 to 0.98). In one PCT of aripiprazole, five treatment subjects reported akathisia compared to no placebo subjects. Olanzapine was significantly associated with fatigue (OR 2.98, 95 percent CI: 1.72 to 5.35). One PCT each of risperidone and ziprasidone reported numbers for fatigue: No placebo subjects reported fatigue compared to one risperidone subject and three ziprasidone subjects.

One large observational study reported lower odds of diabetes in risperidone subjects than in placebo subjects (OR= 0.21, 95 percent CI: 0.07 to 0.51). There was no difference between placebo and olanzapine or quetiapine in diabetes rates.

Adverse event reports for the atypical antipsychotic medications were compared to those for conventional antipsychotics, mood stabilizers, SRIs, tricyclic antidepressants, and serotonin-norepinephrine reuptake inhibitors (SNRIs). Olanzapine had a significantly higher risk of sedation than both mood stabilizers and SRIs (OR 2.81, 95 percent CI: 1.59 to 5.07 and OR 6.04, 95 percent CI: 1.95 to 22.41). Olanzapine had a significantly lower risk for sleep disorders than did mood stabilizers (OR 0.43, 95 percent CI: 0.25 to 0.75). One study reported that ziprasidone had higher odds of causing gastrointestinal disorders, general neurological disorders, fatigue, agitation, and sleep disorders than did SRIs.

We were able to compare adverse events in conventional versus atypical antipsychotics in a couple of trials and observational studies. In two pooled studies, weight gain was more common among olanzapine patients than those taking conventional antipsychotics (OR 2.59, 95 percent CI: 2.02, 3.34). In one large observational study, olanzapine patients were less likely to observe cardiovascular symptoms, fever / infection, gastrointestinal, musculoskeletal, and constitutional problems. Olanzapine patients were also less likely to experience the neurological symptoms fatigue, akathisia, extrapyramidal side effects, and sedation in this study. In one trial of aripiprazole versus conventional antipsychotics, fewer aripiprazole patients experienced akathisia (OR 0.44, 95 percent CI: 0.33, 0.60) and extrapyramidal side effects (OR 0.24, 95 percent CI: 0.18, 0.32).

Examining the head-to-head trials, we found that few adverse events were reported in more than one study. Olanzapine was associated with a higher occurrence of weight gain but a lower occurrence of psychotic events, when compared to ziprasidone. Olanzapine had a higher risk for precipitating diabetes than did risperidone. When compared with risperidone, quetiapine had higher odds of decreased salivation, neurological events, sedation, and agitation.

Six studies compared an atypical antipsychotic plus a conventional drug to the conventional drug alone. In two studies, quetiapine administered with an SRI had a significantly higher risk of producing sedation than did the SRI alone (OR 9.32 95 percent CI: 2.16, 58.89). In one study, quetiapine plus paroxetine had lower odds of anxiety and sleep disorders than paroxetine alone. In one study of 36 subjects, five subjects taking the SRI alone reported headaches compared to none taking the SRI plus risperidone. 17 of the 20 patients taking the SRI plus risperidone reported sedation, compared to 8 of 16 taking the SRI alone.

## Schizophrenia

Because of the paucity of data directly comparing adverse events among atypical antipsychotics prescribed for off-label uses outside of dementia, we reviewed the results of the CATIE trial, a multi-center study at 57 US sites that randomized 1,493 patients with chronic schizophrenia (the indicated condition for these drugs) to receive either olanzapine, quetiapine, risperidone, ziprasidone, or the conventional antipsychotic, perphenazine.<sup>123</sup> This study found that risperidone had the lowest rate of treatment discontinuation due to intolerable side effects (10 percent), whereas olanzapine had the highest rate (18 percent). More patients treated with perphenazine discontinued treatment due to extrapyramidal effects than did those treated with any of the atypical antipsychotics (8 percent vs. 2-4 percent). However, there were no significant differences among the groups in the incidence of extrapyramidal side effects, akathisia, or movement disorders, as measured by the AIMS Global Severity Score, the Barnes Akathisia Rating Scale, or the Simpson-Angus Extrapyramidal Signs Scale. Weight gain was more common in patients treated with olanzapine (average weight gain of two lbs. per month) than in other patients. Two to three times as many patients in the olanzapine-treated group gained 7 percent or more of their baseline body weight as in the other groups. More patients discontinued therapy with olanzapine due to weight gain or metabolic effects than those treated with other drugs (9 percent vs. 1-4 percent). Adverse changes in glycosylated hemoglobin, cholesterol, and triglycerides were also more likely in olanzapine-treated patients than in those treated with the other drugs, while changes in blood glucose level were also greater in olanzapine-treated patients, but the difference did not reach statistical significance. Only risperidone was associated with increasing prolactin levels. Quetiapine treated patients had higher rates of anticholinergic effects (such as dry mouth) than the other drugs, whereas patients treated with olanzapine or quetiapine had lower rates of insomnia than did patients in the other groups. Although the CATIE trial has been critiqued for the dropout rate and the perception that the dose of olanzapine used was comparatively higher than the dose for the other atypical antipsychotics, these data support the findings from the clinical trials of atypical antipsychotics for off-label indications that olanzapine causes the most weight gain but is associated with lower rates of insomnia and that treatment with atypical antipsychotics results in fewer extrapyramidal side effects and movement disorders than does treatment with conventional antipsychotics.

Tardive dyskinesia is a potentially irreversible long-term adverse effect of treatment with conventional antipsychotics. Because the development of tardive dyskinesia is associated with

extrapyramidal side effects, and these side effects are less common among patients treated with atypical antipsychotics, tardive dyskinesia itself is believed to be less common in patients treated with the atypicals. In general the RCTs reviewed in this evidence report were of insufficient duration to detect differences in the rates of development of tardive dyskinesia (there were only six RCTs of at least 1 year's duration). In the CATIE study (reviewed above), which followed patients for 18 months, there was no difference among atypical antipsychotics or between atypical antipsychotics and perphenazine in the Abnormal Involuntary Movement Scale (AIMS) Global Severity score.<sup>123</sup> However, a systematic review of RCTs of atypical antipsychotics that lasted at least 1 year and that reported on new cases of tardive dyskinesia or dyskinesia concluded, based on 11 trials that assessed risperidone, olanzapine, quetiapine, amisulpride, or ziprasidone and involved a total of 2,769 patients, that the weighted-mean annual incidence of tardive dyskinesia for the atypical antipsychotics was 0 percent in children, 0.8 percent in adults, 6.8 percent in a mixed population of adults and elderly, and 5.3 percent in patients 54 years of age and older.<sup>124</sup> In comparison, the weighted-mean annual tardive dyskinesia risk for haloperidol in three RCTs involving adults was 5.4 percent. Statistical testing of differences between groups was not performed in this meta-analysis. However, we performed our own fixed-effects pooled analysis of two of the three RCTs that directly compared an atypical antipsychotic to haloperidol. Our pooled analysis yielded an odds ratio of 0.40 (95 percent CI: 0.22, 0.72), meaning that the atypical antipsychotic medications were significantly less likely to lead to tardive dyskinesia. However, the authors of the meta-analysis note that in the three RCTs that compared atypical antipsychotics with haloperidol, the doses of haloperidol were higher than generally considered appropriate. The authors concluded that these data support the hypothesis that second generation antipsychotics have a lower risk of tardive dyskinesia than first generation antipsychotics at higher doses but called for more carefully designed trials.<sup>124</sup> A recent trial, available in abstract form only,<sup>74</sup> reported that among 293 highly selected patients who primarily had dementia with agitation (of whom only about half completed the trial), those randomized to olanzapine had a lower rate of developing persistent tardive dyskinesia than patients randomized to conventional antipsychotic therapy for up to 1 year (2.5 percent vs. 5.5 percent, respectively), although this difference was not statistically significant ( $p=0.204$ ). These results agree well with our pooled analysis that the atypical antipsychotics have an odds ratio for developing tardive dyskinesia that is about half that of conventional antipsychotics.

## Summary

In summary, there is consistent high-quality evidence across multiple trials that olanzapine is associated with more weight gain than placebo, typical antipsychotics, or other atypical antipsychotics. Evidence about weight gain for other atypical antipsychotics is not as robust.

There is also moderate-grade evidence from multiple trials that the atypical antipsychotics are associated with a greater risk (compared with placebo) of the constellation of symptoms such as confusion, dizziness, somnolence, and sedation.

Although the evidence from off-label uses is insufficient to draw conclusions, limited evidence from patients with schizophrenia suggests that atypical antipsychotics are associated with less tardive dyskinesia than are high doses of haloperidol. The grade of evidence for this outcome is low. There is moderate to strong evidence that most atypical antipsychotics are associated with an increase in extrapyramidal signs or symptoms (excluding tardive dyskinesia) relative to placebo. The CATIE-AD trial concluded that EPS are more common with olanzapine

and risperidone than quetiapine. There is also low-grade evidence that, in adults, the atypical antipsychotics aripiprazole and olanzapine are associated with a lower risk of extrapyramidal side effects than are conventional antipsychotics.

There is moderate-quality evidence from meta-analyses that the use of atypical antipsychotics is associated with an increased risk of death in elderly patients with dementia and agitation. Although these results come from numerous RCTs that are all direct and consistent, this outcome receives this grade because we expect further research is likely to have an important impact on our confidence in the estimate or effect and may change the estimate. For risperidone and olanzapine, this outcome may be due to an increased risk of stroke. Conventional antipsychotic drugs also increase the risk of death in similar patients; however, the grade of evidence for this outcome is low. Other differences in adverse events/safety between atypical antipsychotics and conventional antipsychotics or placebo were either small or inconsistent.

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

### Key Point

There was insufficient information to answer this question. Therefore, it is included as a topic for future research

# Summary and Discussion

In this chapter, we describe the limitations of our review and meta-analysis and then present our conclusions. We also discuss the implications of our findings for future research.

## Limitations

### Publication Bias

Our literature search procedures were extensive and included canvassing experts from academia and industry regarding studies we may have missed. However, our test for possible publication bias indicates that there is unexplained heterogeneity, one reason for which could be publication bias. Furthermore, when we reviewed the recent meta-analysis assessing death and the use of these drugs in persons with dementia, we learned of the existence of some manufacturer-supported trials, the published results of which we searched for and were not able to find, despite extensive computerized searches and requests to the manufacturers (we have since learned the results were not published). It is possible that other such unpublished trial results exist for the other conditions included in our report. We assume that publication bias may occur for all conditions, resulting in an overestimation of the efficacy of these drugs for all conditions.

### Study Quality

An important limitation common to systematic reviews is the quality of the original studies. Recent attempts to define elements of study design and execution that are related to bias have shown that in many cases, such efforts are not reproducible and do not distinguish studies based on result bias. Therefore, the current approach is to avoid rejecting studies or using quality criteria to adjust the meta-analysis results. However, we did use as a measure of quality the Jadad scale, which is the only validated set of quality criteria for trials. As there is a lack of empirical evidence regarding other study characteristics and their relationship to bias, we did not attempt to use other criteria. However, other aspects of the design and execution of a trial may be related to bias, but we do not yet have good measures of these elements. Even given this limitation, our sensitivity analysis on the relationship between trial quality (as measured using Jadad's scale) and result leads us to conclude that the better quality trials report an effect size 25 percent smaller than do lower quality trials. This finding increases the likelihood that a synthesis of results of all studies - whether narrative or quantitative - is producing inflated estimates of efficacy.

## **Heterogeneity**

In our meta-analysis, we observed evidence of heterogeneity. In an attempt to incorporate any heterogeneity, we used a random effects approach. There were too few trials to perform sensitivity analyses using variables that might account for heterogeneity other than quality (completeness of follow-up, dose, etc.). Further, we are unable to explain most of the heterogeneity. Thus, our pooled results should be interpreted in light of the observed heterogeneity.

## **Applicability of Findings**

Green & Glasgow<sup>125</sup> provide a framework for evaluating the relevance, generalization, and applicability of research. Their framework includes assessing the participation rate, the intended target population, representativeness of the setting, 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). Such highly selective criteria may increase the likelihood of benefit and decrease the likelihood of adverse events in such patients. At best we judge these results to be only modestly applicable to the patients seen in typical office-based care.

## **Conclusions**

With the above limitations in mind, we reached the conclusions displayed in the table below.



**Table 11. Summary of evidence- efficacy**

| Condition   | Strength of Evidence   | Conclusion  |
|---|--|---|
| <b>Behavioral Problems in Dementia</b>  | 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 three 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>  |
| <b>Specific Categories of Depression:</b><br><b>a. Inadequate Response to SRI</b><br><b>b. with psychotic features</b><br><b>c. with bipolar disorder</b> | 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 serotonin reuptake inhibitor (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 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.</li> <li>• For bipolar depression, olanzapine and quetiapine were superior to placebo in one study for each drug, but data are conflicting in two other studies which compared atypical antipsychotics to conventional therapy.</li> <li>• We found no studies of aripiprazole for depression.</li> </ul> |

| Condition  | Strength of Evidence   | Conclusion   |
|--|--|--|
| <b>Obsessive-Compulsive Disorder</b>                 | 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 nine 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> <li>We found no trials of ziprasidone or aripiprazole for obsessive-compulsive disorder.</li> </ul>  |
| <b>Post-traumatic Stress Disorder</b>                | Low for risperidone for combat-related PTSD due to sparse data; very low for risperidone and olanzapine for treating PTSD due to causes other than combat. | <ul style="list-style-type: none"> <li>We found four risperidone and two olanzapine trials of over six 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>  |
| <b>Personality Disorders</b>                         | Very low due to small effects, small size of studies, and limitations of trial quality.  | <ul style="list-style-type: none"> <li>Four 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 one small 9- week trial.</li> <li>Aripiprazole was more effective than placebo for the treatment of borderline personality in one small 8-week trial.</li> </ul> |
| <b>Tourette's Syndrome in Children / Adolescents</b> | Low for risperidone; very low for ziprasidone.   | <ul style="list-style-type: none"> <li>We found four trials of risperidone and one 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>  |
| <b>Autism in Children / Adolescents</b>              | 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 eight 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>   |

**Table 12. Summary of adverse event and safety findings for which there is moderate or strong evidence**

| <b>Side effect</b>   | Head to head trials   | Active control trials                                       | Placebo controlled trials  |
|--|---|---|--|
| <b>Mortality (dementia patients only)</b>  | Insufficient evidence of difference.                          | Insufficient evidence of difference.                        | Small but significant increased risk for atypical antipsychotics compared to placebo.                                  |
| <b>Cardiovascular (not including cerebrovascular accident)</b>                   | Insufficient evidence of difference.                          | Insufficient evidence of difference.                        | Insufficient evidence of difference.   |
| <b>Cerebrovascular accident (dementia patients only)</b>                         | Insufficient evidence of difference.                          | Insufficient evidence of difference.                        | Small but significant increased risk for risperidone and olanzapine compared to placebo.                               |
| <b>Extrapyramidal symptoms</b>   | 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. |
| <b>Neurological (fatigue, headaches, dizziness; excludes movement disorders)</b> | Insufficient evidence of difference.                          | Insufficient evidence of difference.                        | More common in risperidone, olanzapine and aripiprazole than placebo, other drugs insufficiently studied.              |
| <b>Sedation</b>  | Insufficient evidence of difference                           | More common in olanzapine than mood stabilizers.            | More common in atypical antipsychotics than placebo.   |
| <b>Weight gain</b>   | 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.                            |



## Future Research

More research is urgently needed about how to safely treat agitation in dementia. 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 reported increase in risk of death in patients treated with atypical antipsychotics was small, the demonstrable benefits in the RCTs we identified were also small. Furthermore, we need to understand whether the increased risk of death is associated with all antipsychotics drugs. Recent observational studies from the DEcIDE program suggest that typical (conventional) antipsychotics may have an even greater risk than atypical antipsychotics. Part of this research program is going to require new clinical trials that measure benefit and are also appropriately powered to detect an increased risk of death - which will require very large sample sizes. Without measuring this risk of death in the same trials used to measure benefit, we will continue to be forced to rely on indirect--rather than direct--methods to compare risks and benefits. The results of the CATIE-AD study have added substantially to our knowledge about use of atypical antipsychotics in patients with dementia. We await the results of phase 2 of CATIE-AD.

Related to the above question, but not limited to dementia per se, is the need for studies comparing the development of extrapyramidal symptoms--particularly tardive dyskinesia--between patients taking atypical antipsychotics and those taking typical doses of conventional antipsychotics. Understanding how drug dose and age influence the occurrence of death or extrapyramidal symptoms/tardive dyskinesia would help estimate possible risks in specific populations.

With few exceptions, there is insufficient high-grade evidence to reach conclusions about the efficacy of atypical antipsychotic medications for any of these off-label indications, compared with placebo or active therapy. If atypical antipsychotic medications are going to be used for these indications, then trial evidence is necessary for clinicians, patients, and policymakers to predict the expected benefits.

More head-to-head trials are needed to compare atypical antipsychotics for conditions other than dementia. While the evidence we reviewed does not support the likelihood of major differences in efficacy between atypical antipsychotics, this hypothesis still needs rigorous testing.

Greater agreement is needed about which outcomes to report for most all of these conditions to facilitate easier comparisons across trials. Specifically, it would be useful to have agreement on the most important outcomes for each condition.



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