

Drug Class Review

Atypical Antipsychotic Drugs

Final Report Update 2
Executive Summary

May 2008



The purpose of this report is to make available information regarding the comparative effectiveness and safety profiles of different drugs within pharmaceutical classes. Reports are not usage guidelines, nor should they be read as an endorsement of, or recommendation for any particular drug, use or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

Marian S. McDonagh, PharmD
Kim Peterson, MS
Susan Carson, MPH
Benjamin Chan, MS
Sujata Thakurta, MPA:HA

Oregon Evidence-based Practice Center
Oregon Health & Science University
Mark Helfand, MD, MPH, Director



INTRODUCTION

“Atypical” antipsychotic agents were originally designed to treat the symptoms of schizophrenia and bipolar disorder. In general, atypical antipsychotics produce antipsychotic responses with fewer acute extrapyramidal side effects than conventional antipsychotic drugs. Atypical antipsychotics may also treat negative symptoms and improve cognitive functioning. Clozapine, the prototypic atypical antipsychotic, was introduced in 1989. Since then, six other atypical antipsychotics have been introduced: risperidone (1993), olanzapine (1996), quetiapine (1997), ziprasidone (2001), aripiprazole (2002), and paliperidone (2006). This review addresses the use of atypical antipsychotics to treat schizophrenia, bipolar disorder, behavioral disturbances associated with dementia, autistic disorder, and disruptive behavior disorder.

Scope and Key Questions

The purpose of this review is to help policymakers and clinicians make informed choices about the use of atypical antipsychotics. Given the prominent role of drug therapy in psychiatric disease, our goal is to summarize comparative data on the efficacy, effectiveness, tolerability, and safety of atypical antipsychotics.

The participating organizations approved the following key questions to guide this review:

Key Question 1. For adults with schizophrenia, related psychoses, or bipolar disorder (manic or depressive phases, rapid cycling, mixed states), do the atypical antipsychotic drugs differ in benefits (efficacy, effectiveness) or harms?

a. For adults experiencing a first episode of schizophrenia, do the atypical antipsychotic drugs differ in benefits (efficacy, effectiveness) or harms?

b. For adult patients with schizophrenia, related psychoses (including first episode), or bipolar disorder, what is the comparative evidence that differences in adherence or persistence among the atypical antipsychotic drugs correlates with a difference in clinical outcomes?

Key Question 2. For children and adolescents with pervasive developmental disorders or disruptive behavior disorders, do the atypical antipsychotic drugs differ in benefits (efficacy, effectiveness) or harms?

Key Question 3. For older adults with behavioral and psychological symptoms of dementia, do the atypical antipsychotic drugs differ in benefits (efficacy, effectiveness) or harms?

Inclusion Criteria

Populations

Populations comprised adults with schizophrenia, schizoaffective disorder, schizophreniform disorder, bipolar disorder, or behavioral and psychological symptoms of dementia and children and adolescents (under age 18) with autism or disruptive behavior disorders.

Interventions

Interventions included aripiprazole, clozapine, olanzapine, paliperidone, quetiapine, risperidone, and ziprasidone.

Outcomes

Effectiveness and efficacy outcomes included primarily mortality, symptoms, functional capacity, and hospitalization. Safety outcomes included overall adverse events, withdrawals due to adverse events, serious harms, and specific adverse events (for example, extrapyramidal effects, weight gain, or diabetes mellitus).

Study designs

For effectiveness, controlled clinical trials, comparative observational studies (cohort studies, including database studies, and case-control studies), and good-quality systematic reviews were included. For efficacy, head-to-head randomized controlled trials and good-quality systematic reviews were included. If no direct head-to-head evidence existed, placebo-controlled and active control (conventional antipsychotics) trials were included. For safety, in addition to controlled clinical trials comparative observational studies and single intervention observational studies with 2 years or more exposure time were included.

METHODS

To identify relevant citations, we searched the Cochrane Central Register of Controlled Trials (4th Quarter 2007), MEDLINE (1950 to week 1 November 2007), and PsycINFO (1985 to week 2 November 2007) using terms for included drugs, indications, and study designs. We attempted to identify additional studies by searching reference lists of included studies and reviews, hand searching medical and statistical reviews published on the FDA web site, and searching dossiers submitted by pharmaceutical companies for the current review.

All potentially relevant full-text articles identified from literature searches were assessed for inclusion. Data abstracted from included trials were study design, setting, population characteristics, eligibility and exclusion criteria, interventions, comparisons, numbers screened, eligible, enrolled, and lost to follow-up, method of outcome ascertainment, and results for each outcome. Dual assessment by independent reviewers was used for all processes, with involvement of a third party leading to consensus regarding disagreements.

We rated the internal validity of each trial based on the methods used for randomization, allocation concealment, and blinding; the similarity of compared groups at baseline; maintenance of comparable groups; adequate reporting of dropouts, attrition, crossover, adherence, and contamination; loss to follow-up; and the use of intention-to-treat analysis. Observational studies were also assessed for quality. The criteria reflect aspects of the study design that are particularly important for assessing adverse events. Studies were then rated good, fair, or poor quality.

We obtained peer review of the initial draft of this report from 11 content or methodology experts and 4 professional or patient advocacy organizations. For the first updated version of this report, we requested peer review from 10 content experts and representatives of professional or patient advocacy organizations. We received comments from 6. For the second update of this report, we have received peer review from 2 clinical and methodological experts who reviewed the report in its previous versions. Their comments were reviewed and, where possible,

incorporated into the final document with final decisions made by the DERP participating organizations.

RESULTS

After applying the eligibility and exclusion criteria to titles and abstracts found through our searches and received in dossiers from pharmaceutical manufacturers Janssen Pharmaceutica (risperidone), Eli Lilly and Company (olanzapine), and Novartis Pharmaceuticals (clozapine), for the original report (September 2005) we obtained full-paper copies of 1077 citations. After applying the criteria for inclusion, we ultimately included 270 publications.

In Update 1 (April 2006) the scope of our report changed to include studies on inpatients, observational studies, and short-term studies evaluating the efficacy of the short-acting intramuscular forms of the atypical antipsychotics. Of 3613 citations, we obtained full-paper copies of 1833 studies and included 589 studies in the report. For Update 1 we received dossiers from Eli Lilly and Company (olanzapine), AstraZeneca (quetiapine), and Bristol-Myers Squibb (aripiprazole).

For Update 2 our scope again has changed somewhat, this time to include patients with first-episode schizophrenia, to include new formulations and a new drug, and, based on our experience with the non-randomized controlled trial literature in Update 1, to limit the inclusion of uncontrolled studies to those with long-term followup.

Schizophrenia and Related Psychoses

Summary of Evidence for Comparative Effectiveness and Short Term Adverse Events of Atypical Antipsychotics in Patients with Schizophrenia

The largest body of evidence exists for clozapine, olanzapine and risperidone. More- limited evidence exists for aripiprazole, quetiapine and ziprasidone, and very limited evidence exists for paliperidone.

Only 5 studies were effectiveness trials. The remainder of the direct evidence came from efficacy trials, which included narrowly defined patient populations and were not conducted within the context of a care system with a typical range of co-interventions, and/or co-morbidities, and a small number of studies with observational designs (for example, cohort or case-control). The generalizability of the findings of the efficacy studies to broader groups of patients and settings is limited. Limited additional information was gained from indirect comparisons using placebo- or conventional antipsychotic-controlled trials or observational studies with no comparison to another atypical antipsychotic. Evidence for clozapine is largely in treatment-resistant populations.

Clozapine was superior to olanzapine in preventing suicidality, including suicide attempts (successful or not) or worsening suicidal behavior, in patients at high risk of suicide (number needed to treat = 12). This study also reported significantly greater rates of weight gain with olanzapine compared with clozapine (number needed to harm = 4).

Risk of relapse appears to be lower with olanzapine than quetiapine over 1 and 3 years of followup. Results favor olanzapine over risperidone in a 28-week trial and a 3-year observational study, but differences were not found in another observational study with 1 year of followup.

Good-quality trial evidence indicates lower risk of hospitalization with olanzapine compared with quetiapine, risperidone, and ziprasidone. Observational study results were conflicting.

Good-quality trial evidence did not differentiate olanzapine, quetiapine, risperidone, or ziprasidone in quality-of-life measures, although improvements were seen with all the drugs. Observational evidence was mixed with some indicating a potential for olanzapine to result in larger improvements depending on the scale used. Limited evidence from a single trial found olanzapine to result in better social function compared with risperidone; however, observational evidence conflicts with these findings.

The rate of drug discontinuation and time to discontinuation are summary values that represent the net effect of the 2 main causes of discontinuations, lack of efficacy and adverse events. Olanzapine has lower drug discontinuation rates than aripiprazole, quetiapine, risperidone, and ziprasidone, with numbers needed to treat of 10 to 21 based on mixed-treatment comparison analysis of multiple trials, controlling for within-study differences in dose levels. This analysis includes patients with a first episode of schizophrenia symptoms and patients with treatment-resistant symptoms. The results for these populations are consistent with the overall results. Clozapine was found to have lower discontinuation rates than these drugs, based on mixed-treatment comparison analysis of trials of patients mostly with treatment-resistant symptoms. Numbers needed to treat based on CATIE for olanzapine compared with quetiapine, risperidone, or ziprasidone range from 6 to 10. Olanzapine also was found to have longer time to discontinuation than quetiapine, risperidone, and ziprasidone. Under trial circumstances, the difference was approximately 4 months longer with olanzapine, while observational studies indicate a much smaller difference, around 40 days longer. Limited evidence indicates that clozapine may have longer time to discontinuation than olanzapine. Mixed-treatment comparisons analysis controlling for within-study dose comparisons indicate higher odds of discontinuing drug due to adverse events with clozapine than with olanzapine, quetiapine, and risperidone. Higher rates were also seen with olanzapine than with quetiapine and risperidone. Differences were not found with clozapine or olanzapine compared with paliperidone or ziprasidone, although smaller sample sizes and indirect comparisons may have limited the ability to find a difference.

Evidence on inpatient outcomes is mixed. Two studies found clozapine resulted in lower aggression scores compared with olanzapine or risperidone, although one study found this only with physical aggression, and the other found the difference only after allowing time to reach full doses of clozapine. No differences were found in rates of overall discontinuation of prescribed drug, although pooled data from four retrospective studies found risperidone superior to olanzapine in the risk of discontinuation due to lack of efficacy (number needed to treat = 30) or due to adverse events (number needed to harm = 65). Four of 7 studies reporting length of stay found no statistically significant difference between olanzapine and risperidone. Evidence is conflicting, with 3 observational studies and 1 trial indicating a faster onset of efficacy with risperidone than with olanzapine, but 1 trial finding no statistically significant difference. Data for quetiapine, aripiprazole, and ziprasidone were too minimal for conclusions to be drawn, and no data on paliperidone was found.

Consistent differences in *efficacy* were not found between clozapine, olanzapine, quetiapine, risperidone, ziprasidone, or aripiprazole in shorter-term trials of inpatients or outpatients. When the criterion for response is > 20% improvement in the Positive and Negative Symptom Scale (PANSS), response rates range from 45% to 80%. Variations in patient population and duration of treatment account for the broad range. Pooled analysis of response

rates did not indicate statistically significant differences between the drugs. Exceptions exist for individual studies where the definition of response is varied. Limited evidence did not identify statistically significant differences between risperidone long-acting injection and oral risperidone or olanzapine. Only indirect evidence from placebo- or haloperidol-controlled trials is available for extended-release paliperidone, extended-release quetiapine, and olanzapine or ziprasidone injection.

Rates of extrapyramidal side effects and measures of severity of symptoms were not found to be different among the drugs in most trials. Small numbers of studies found worse extrapyramidal side effect outcomes with risperidone than with olanzapine, clozapine, or quetiapine, although the specific measures on which risperidone performed worse were not consistent across these studies. Clozapine and ziprasidone were also found to have worse outcomes than olanzapine on a limited number of outcomes in a few trials. Evidence for aripiprazole and paliperidone is too limited to make conclusions.

Weight gain in clinical trials was greater with olanzapine than the other atypical antipsychotics, in the range of 7 to 10 pounds more, depending on the comparison group and baseline risk. The other drugs appear to cause weight gain in the following order: clozapine > quetiapine ~ risperidone > ziprasidone and aripiprazole. This assessment is based on trials directly comparing these drugs, rather than indirect comparisons from trials comparing atypical antipsychotics with conventional antipsychotics, which may indicate clozapine causes weight gain similar to or greater than olanzapine. Ziprasidone causes the least impact on weight, with most studies showing modest weight loss. Similarly, the proportion of patients with clinically significant weight gain (> 7% body weight) is statistically significantly higher with olanzapine than the other drugs. Data for paliperidone are too limited to make conclusions. The largest body of evidence for direct comparison of weight gain compares olanzapine with risperidone, where the pooled estimate indicates a mean of 7 pounds greater weight gain with olanzapine. The pooled relative risk of clinically significant weight gain with olanzapine is 2.26 compared with risperidone, with a number needed to treat of 7. For every 7 people treated with olanzapine rather than risperidone, 1 additional patient will have weight gain of > 7% of body weight.

Olanzapine and clozapine cause greater increases in triglycerides than quetiapine or risperidone. Olanzapine also was found to cause increases in triglycerides, low-density lipoprotein cholesterol, and total cholesterol while ziprasidone had little or no effect. An increase in triglycerides (but not total cholesterol or low-density lipoprotein cholesterol) and a decrease in high-density lipoprotein cholesterol was found with olanzapine when compared with aripiprazole. Increases in triglycerides range from 26 to 79 mg/dL with olanzapine. Clozapine results in higher rates of somnolence than risperidone; quetiapine results in higher rates of somnolence, dizziness, and dry mouth than risperidone; and clozapine results in higher rates of somnolence, dizziness, and hypersalivation than olanzapine. Differences in these adverse events were not found between olanzapine and risperidone. Evidence on sexual dysfunction as an adverse event is limited but indicates fewer reports or less severe symptoms with quetiapine or ziprasidone than with risperidone.

The sponsorship of individual trials by pharmaceutical companies appears to be associated with positive findings on at least one outcome measure. Trials sponsored by pharmaceutical companies also tended to use nonequivalent mean doses between the drugs under comparison. Concerns about inequitable mean dose comparisons draw into question the effectiveness of blinding among those involved in titrating doses. Many of the outcomes assessed

involve subjectivity on the part of the assessor, so failure of blinding is a serious concern for outcome measurement.

Very limited evidence exists regarding atypical antipsychotics used for the treatment of schizophrenia in subgroup populations. Differences between olanzapine and risperidone in efficacy measures or quality of life were not seen based on age (greater than 60 years or 50-65 years compared with younger populations). With both olanzapine and risperidone, women and patients less than 40 years old were found to be at higher risk of new-onset diabetes than older patients (compared with conventional antipsychotics). Limited evidence suggests Mexican American and African American patients discontinue their prescribed atypical antipsychotic 18-19 days earlier than white patients, but an effect of specific drug (olanzapine or risperidone) was not found.

Bipolar Disorder

Summary of Evidence for Comparative Effectiveness and Short-term Adverse Events of Atypical Antipsychotics in Patients with Bipolar Disorder

Olanzapine is the most well-studied atypical antipsychotic as maintenance therapy for bipolar disorder. Olanzapine was superior to placebo and comparable to lithium and divalproex in preventing relapse in 47- to 52-week trials. Aripiprazole and quetiapine have also shown potential for use as maintenance therapy. Hospitalization risk was lower for quetiapine than for olanzapine or risperidone in a retrospective database study of 10 037 patients.

Aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone monotherapies all have been shown to be superior to placebo on Young Mania Rating Scale (YMRS)-based efficacy outcomes for acute mania. As add-on therapy, olanzapine, quetiapine, and risperidone, but not ziprasidone, were superior to placebo on YMRS-based efficacy outcomes for acute mania. Compared with placebo, rates of symptom remission (YMRS \leq 12) were consistently higher for olanzapine and quetiapine when added to lithium or valproate/divalproex and higher for quetiapine and risperidone when used as monotherapy. Quetiapine and olanzapine were the only atypical antipsychotics shown to be superior to placebo in reducing depressive symptoms in patients with predominantly bipolar I depression. In a post hoc analysis of combined data from two similarly designed trials, greater reductions in depressive symptoms were also found for quetiapine compared with placebo in subgroups of patients with bipolar II depression. In 24-hour studies of acute agitation, greater reductions in 2-hour PANSS Excited Component scores were found for the intramuscular forms of aripiprazole and olanzapine compared with lorazepam and haloperidol, respectively. No such studies were found for the intramuscular form of ziprasidone.

Olanzapine and quetiapine each differed from risperidone in adverse events but not primary efficacy outcomes in head-to-head trials: In a small 2-day trial, more had adverse events with low dosages of quetiapine than risperidone, and adverse cognitive effects and somnolence were worse with quetiapine. Three-week weight increases were greater with olanzapine, while increased serum prolactin and sexual dysfunction were more likely with risperidone. Extrapyramidal symptoms were consistently worse for aripiprazole and ziprasidone than placebo and worse for risperidone compared with placebo on some, but not all, extrapyramidal symptom-related outcomes. Compared with placebo, weight gain was greater with olanzapine, quetiapine, and risperidone, but not for aripiprazole or ziprasidone.

A retrospective case-control study comparing atypical antipsychotics with conventional antipsychotics found statistically significant increases in risk of development or exacerbation of

diabetes mellitus for clozapine (hazard ratio 7.0, 95% CI 1.7-28.9), risperidone (hazard ratio 3.4, 95% CI 2.8-4.2), olanzapine (hazard ratio 3.2, 95% CI 2.7-3.8), and quetiapine (hazard ratio 1.8, 95% CI 1.4-2.4). The increase associated with ziprasidone was not statistically significant (hazard ratio 1.68, 95% CI 0.84-3.36). Results were mixed across two retrospective claims database studies that directly compared persistence outcomes for olanzapine, quetiapine, risperidone, and ziprasidone.

The only evidence about use of atypical antipsychotics in patients with rapid cycling bipolar disorder comes from subgroup analyses. When the most recent episode was manic or mixed greater improvement in mean YMRS score was seen with aripiprazole and olanzapine than placebo. Clozapine was no better than chlorpromazine as acute monotherapy over 3 weeks in inpatients with manic or mixed episodes. No trials of paliperidone in patients with bipolar disorder were found. Evidence was insufficient for drawing any conclusions about comparative effectiveness or safety in subgroups of patients based on age, gender, or comorbidities.

Behavioral and Psychological Symptoms of Dementia

Summary of Evidence for Comparative Effectiveness and Short-term Adverse Events of Atypical Antipsychotics in Patients with Behavioral and Psychological Symptoms of Dementia

Seven head-to-head trials compared one atypical antipsychotic to another in patients with behavioral and psychological symptoms of dementia. The best evidence for comparative effectiveness comes from the Alzheimer disease arm of the CATIE trial (CATIE-AD), which found similar rates of withdrawals and response for olanzapine, risperidone, and quetiapine. Five head-to-head trials compared olanzapine with risperidone and all but one was rated poor quality. The 1 fair-quality study found no difference between olanzapine and risperidone or between drug and placebo on the Neuropsychiatric Inventory, Clinical Global Impressions scale, Brief Psychiatric Rating Scale, and Cohen-Mansfield Agitation Inventory after 10 weeks. A fair-quality study found no difference in efficacy between quetiapine and olanzapine. In placebo-controlled trials, results for efficacy of aripiprazole, olanzapine, risperidone, and quetiapine were mixed. These studies do not provide comparative evidence due to differences in outcome measures and other factors.

The CATIE-AD trial found no difference between active treatment groups or between any treatment group and placebo in overall withdrawals. All treatment groups had higher rates of withdrawals due to intolerability, adverse events, or death compared with placebo, but there was no difference between treatment groups for this outcome. Other short-term head-to-head trials found similar rates of withdrawals and adverse events for olanzapine and risperidone, and for quetiapine and risperidone.

No conclusions about comparative effectiveness or safety based on age, gender, or comorbidities can be made from this body of evidence.

Children and Adolescents with Autism, Disruptive Behavior Disorders, or Attention Deficit Hyperactivity Disorder

Summary of the Evidence for Comparative Effectiveness and Short-term Adverse Events of Atypical Antipsychotics in Children and Adolescents

The comparative evidence in children and adolescents is poor. No head-to-head trials have been reported. No effectiveness trials exist.

Children and adolescents with autism

Risperidone (5 trials) and olanzapine (1 trial) were superior to placebo for improving behavioral symptoms in children with autism and other pervasive developmental disorders. Olanzapine was similar in efficacy to haloperidol in one small study. Quetiapine for children with autism or disruptive behavior disorders has been studied only in small, short-term, uncontrolled studies or retrospective observational studies that did not meet inclusion criteria for this review. There are no trials of other atypical antipsychotics in this population. Conclusions about comparative efficacy cannot be drawn from this body of evidence because trials varied in population, duration of treatment, and outcome measures used.

Children and adolescents with disruptive behavior disorders

Five fair-quality, short-term placebo-controlled trials found risperidone superior to placebo. One of these was conducted in hospitalized adolescents and the rest in outpatients. No evidence has been reported for other atypical antipsychotics.

Weight gain reported in short-term trials ranged from 2.7 kg to 5.7 kg. Weight gain was significantly greater with risperidone than placebo in 3 trials and greater with olanzapine than haloperidol in 1 trial. In a Cochrane meta-analysis of 2 trials of risperidone in children with autism, the mean difference in weight gain for risperidone compared with placebo was 1.78 kg (95% CI 1.15-2.41). The incidence of extrapyramidal symptoms and other adverse events was low in short-term trials.

Longer-term safety

No comparative evidence exists; only risperidone has been studied. Evidence includes three 6-month placebo-controlled trials and 4 open-label extension studies of short-term efficacy trials. Weight gain ranged from 2.1 kg to 5.6 kg in studies up to one year. In a 2-year open-label extension study of 14 children, mean weight gain was 8.09 kg. Other adverse events were infrequent.

Subgroups

No conclusions about comparative effectiveness or safety based on age, gender, or comorbidities can be made from this body of evidence.

Serious Harms

Summary of Evidence

Although observational studies provide some estimate of the prevalence of serious longer-term and/or serious adverse events with individual atypical antipsychotics, few studies provide

comparative data across atypical antipsychotics for any one adverse event. The overall body of evidence is low quality due to a variety of flaws in design and analysis should be interpreted with caution.

Mortality. Limited evidence from one comparative study found an increased risk of all-cause mortality among patients with schizophrenia who had taken risperidone compared with those taking clozapine. Limited evidence in elderly patients found an increased risk of mortality with olanzapine compared with conventional antipsychotics, but no statistically significant increase with clozapine or risperidone. Other evidence on mortality is non-comparative, although an FDA analysis found an increased risk of mortality with all atypical antipsychotics in older patients with dementia.

Cerebrovascular events. Data from trials indicates an elevated risk of stroke with olanzapine and risperidone among older patients with dementia. Observational evidence does not indicate a clear increase in risk and finds no difference in risk among the atypical antipsychotics studied (olanzapine, risperidone, quetiapine, and aripiprazole).

Diabetes mellitus. The evidence on the comparative risk of diabetes with atypical antipsychotics is mixed, with a strong correlation between source of funding and positive results for that company's drug. Three of five retrospective cohort studies found a statistically significant increase in risk of new-onset diabetes among olanzapine users compared with risperidone users. Two smaller studies found no differences, including one comparing olanzapine with quetiapine and clozapine. Based on the largest fair-quality study, the risk of diabetes with olanzapine compared with risperidone is greater among women and is highest in the early exposure periods. These studies do not control for several important potentially confounding factors, such as weight or family history of diabetes. The absolute increase in risk is not clear based on this evidence. The comparative evidence regarding the risk of diabetes with clozapine is weak. Only 1 study makes a direct comparison and one allows indirect comparison, with conflicting findings. Indirect evidence does not support an increased risk of diabetes with clozapine compared with conventional antipsychotics in the overall population studied, although there is evidence of an increased risk in women and younger patients. Comparative evidence on the risk of diabetes with quetiapine is very limited, with only two studies. Based on one direct comparison and one indirect comparison, there is no apparent increased risk relative to olanzapine, risperidone, or clozapine. Evidence on the risk of diabetes with paliperidone, ziprasidone, or aripiprazole was not found.

Weight gain. The comparative evidence from 6 long-term studies involving more than 10 000 patients support the findings of the randomized controlled trials. Weight gain is 1-3 kg greater with olanzapine than risperidone. The exact proportions of patients with clinically significant weight gain is less clear, but using a definition of $\geq 7\%$ gain and data from 3 studies, the pooled odds ratio for olanzapine compared with risperidone is 1.88 (95% CI 1.33-2.70) with a number needed to harm of 4. Evidence about the other atypical antipsychotics is too limited for comparisons, although indirect evidence suggests a significant weight gain associated with clozapine.

Due to large differences in study characteristics, it is not possible to draw conclusions about comparative long-term safety through indirect comparisons across observational studies.

Neuroleptic malignant syndrome. No comparative studies were found.

Seizures. Only 2 studies with at least 2 years of follow-up reported rates of seizures associated with clozapine: 2.9% and 4.2%. The association may be related to both dose and duration of exposure.

Tardive dyskinesia. Studies of clozapine suggest rates of tardive dyskinesia of 1% to 7% over 6 to 26 months. Studies of risperidone suggest rates of 0% to 5% over 6 to 26 months. One study found the rate with risperidone (3%) to be statistically significantly greater than with olanzapine (1%) after 6 months. That study found no significant differences in comparisons with quetiapine. In older patients, studies of risperidone showed higher rates of tardive dyskinesia (2.6% to 5%). The incidence was associated with dose in one analysis.

Myocarditis and cardiomyopathy. A large adverse-event database study found that clozapine was significantly associated with myocarditis or cardiomyopathy, while olanzapine, quetiapine, and risperidone were not. Limited evidence suggests an increased risk of cardiac arrest with risperidone compared with clozapine, lower odds of cardiomyopathy with aripiprazole, and increased odds of hypertension with ziprasidone (both compared with conventional antipsychotics), but this evidence is not conclusive.

Agranulocytosis. In 7 studies with 2 to 5 years of follow-up, the reported incidence of agranulocytosis with clozapine ranged from 0% to 5.9%.

Suggested citation for this report:

McDonagh MS, Peterson K, Carson S, Chan B, Thakurta S. Drug class review on atypical antipsychotic drugs. Update #2 Final Report. <http://www.ohsu.edu/drugeffectiveness/reports/final.cfm>