



# **DRUG EFFECTIVENESS REVIEW PROJECT**

## **P&T Committee Brief Drug Class Review on Atypical Antipsychotic Drugs Update 2**

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### **P&T Committee Brief Disclaimer**

This brief was written by the Center for Evidence-based Policy at Oregon Health & Science University (the Center). It is a summary of certain material matters contained in the Drug Effectiveness Review Project (DERP) report "Drug Class Review on Atypical Antipsychotic Drugs Update 2" dated June 2008, which is a product of the OR Evidence-based Practice Center at Oregon Health & Science University. You can find the original report online at the following web address:

[http://www.ohsu.edu/ohsuedu/research/policycenter/customcf/derp/product/AAP\\_final\\_report\\_update\\_27.pdf](http://www.ohsu.edu/ohsuedu/research/policycenter/customcf/derp/product/AAP_final_report_update_27.pdf). Although at least one of the authors of this report reviewed and commented on the brief, its content and conclusions are those of the CEBP and not those of the authors or reviewers of the DERP report. The Center is a policy resource and is not providing any legal or business advice. This Brief is subject to the information and conclusions contained in the DERP report, and readers of this Brief are advised to review the DERP report. This Brief is intended for the benefit of the participant organizations and their constituent decision-making bodies.

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P & T COMMITTEE BRIEF  
Drug Class Review on Atypical Antipsychotic Drugs

**Background:**

“Atypical” antipsychotics (AAPs) are used to treat the symptoms of schizophrenia and bipolar disorder in adults. Clozapine, the prototypic AAP, was introduced in the US in 1989. Since then, six other AAPs have been introduced in the US, five in Canada (Table I). Some AAPs are available in different product formulations. Before the introduction of AAPs to clinical practice, “conventional” antipsychotics (CAPs) [phenothiazine derivatives (e.g. chlorpromazine, perphenazine) and butyrophenone derivatives (e.g. haloperidol)] were used. This review compares the clinical effectiveness of AAPs for the following indications: Schizophrenia, bipolar I disorder, behavioral disturbances associated with dementia, autistic disorder, disruptive behavior disorder (DBD) and pervasive development disorder. The comparison of AAPs and CAPs is beyond the scope of this review.

Table 1

Active Ingredient	Trade Name	Formulations
aripiprazole	Abilify*	Tablet, ODT <sup>1</sup> , liquid, injection
clozapine	Clozaril, Fazaclo*	Tablet, ODT <sup>1*</sup>
olanzapine	Zyprexa, Zyprexa Zydis <sup>1**</sup>	Tablet, ODT <sup>1</sup> , injection
paliperidone	Invega	ER Tablet
quetiapine	Seroquel, Seroquel XR	Tablet, ER Tablet
risperidone	Risperdal, Risperdal M-TAB <sup>1**</sup> , Risperdal Consta	Tablet, ODT <sup>1</sup> , liquid, injection
ziprasidone	Geodon, Zeldox**	Capsule, injection*

<sup>1</sup>Orally disintegrating tablet; ER= Extended-release; \*Product not available in Canada; \*\*Canadian Product

**Methodology:**

The Drug Effectiveness Review Project reviews all pertinent studies, and solicits and accepts public input. This is the second update of this drug class. Study eligibility is determined by pre-set criteria. Studies which did not meet these criteria with respect to study design or duration, patient population, interventions, or outcomes were excluded. Additionally, studies not in English were excluded. The quality of all included studies was appraised.

**Evidence Available:**

Searches identified 5126 citations. Relevant information consists of 615 publications, 198 of them new in this update. Of these, 138 were head-to-head trials, 101 were active controlled trials, 108 were placebo controlled trials, 214 were observational studies and 53 were systematic reviews. Effectiveness outcome measures include mortality, quality of life (QOL), functional capacity and hospitalization (including emergency room visits). Efficacy outcomes include symptom response (rates, duration, speed, remission, relapse and time to discontinuation), adherence, persistence and care-giver burden. Safety outcomes include adverse event (AE) rates, withdrawals and time to withdrawal due to AEs, serious AEs (life-threatening or resulting in long-term morbidity) and specific AEs [e.g. extrapyramidal symptoms (EPSs), weight gain, agitation, constipation, somnolence, hypersalivation, hypotension, elevated serum lipid levels, sexual dysfunction].

**Key Questions and Findings:**

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

**Schizophrenia and Related Disorders**

There were only five *effectiveness trials*, while the remainder of the direct evidence comes from *efficacy trials*, which have limited generalizability. Clozapine was superior to olanzapine in preventing suicidality (number needed to treat = 12), and had lower rates of weight gain (number needed to harm = 4). Risk of relapse of symptoms of schizophrenia appears to be lower with olanzapine than quetiapine, and also appears to be lower compared to risperidone in two studies. In addition, good-quality trial evidence indicates a lower risk of hospitalization with olanzapine compared to quetiapine, risperidone, and ziprasidone, although observational study results were conflicting.

Good-quality trial evidence did not differentiate olanzapine, quetiapine, risperidone, or ziprasidone in QOL measures, although improvements from baseline were seen with all the drugs. Observational evidence is mixed with some studies indicating a potential for olanzapine to result in larger improvements depending on the clinical assessment scale used.

The rate of drug discontinuation and time to discontinuation are summary values that represent the net effect of the two main causes of discontinuation: lack of efficacy and AEs. Both clozapine and olanzapine have lower drug discontinuation rates than aripiprazole, quetiapine, risperidone and ziprasidone. Olanzapine was also found to have longer time to discontinuation than quetiapine, risperidone and ziprasidone. Under trial circumstances, the difference was approximately four months longer with olanzapine, while observational studies indicate a difference of around 40 days longer before treatment discontinuation. Differences were not found with clozapine or olanzapine compared to paliperidone or ziprasidone.

Evidence on inpatient outcomes is mixed. Two studies found clozapine resulted in lower aggression scores compared with olanzapine or risperidone. No differences were found in rates of overall discontinuation of prescribed drug. Four of the seven studies that reported length of stay found no significant difference between olanzapine and risperidone, although pooling the results of the four studies that were similar found a shorter length of stay (five days) with risperidone. Regarding time to onset of efficacy, one trial found no significant difference, while pooling data from three observational studies suggested shorter time to efficacy with risperidone compared to aripiprazole, haloperidol, olanzapine and ziprasidone.

Consistent differences in *efficacy* were not found between clozapine, olanzapine, quetiapine, risperidone, ziprasidone, or aripiprazole in shorter-term trials of inpatients or outpatients. Using the criterion of > 20% improvement in the Positive and Negative Symptom Scale, response rates range from 45% to 80% for clozapine, olanzapine and risperidone. Pooled analysis of response rates did not find significant differences between the drugs. No comparative trials are available for paliperidone, quetiapine, olanzapine and ziprasidone injection.

Short-term harms for patients with schizophrenia are summarized in Table 2 below.

NOTE: 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.

Table 2

Harm	Evidence
EPS	Rates, severity of symptoms not different in most trials
Weight Gain	Greater with olanzapine [by 7-10 pounds (3.2-4.5 kg)] vs. other AAPs More patients gain > 7% of body weight with olanzapine vs. other AAPs For other AAPs: clozapine > quetiapine ~ risperidone > ziprasidone ~ aripiprazole Ziprasidone has least impact, may cause small weight loss
Lipids	Increase in triglycerides greater with olanzapine, clozapine vs. quetiapine, risperidone. Increase in low-density lipoprotein and total cholesterol with olanzapine vs. ziprasidone Decrease in high-density lipoprotein cholesterol with olanzapine vs. aripiprazole
Somnolence	Clozapine > risperidone, olanzapine Quetiapine > risperidone
Dizziness	Quetiapine > risperidone Clozapine > olanzapine
Dry Mouth	Quetiapine > risperidone
Hypersalivation	Clozapine > olanzapine
Sexual Dysfunction	Fewer reports or less severe with quetiapine or ziprasidone vs. risperidone

### **Adult Bipolar Disorders**

Olanzapine was superior to placebo and comparable to lithium and divalproex in preventing relapse. Aripiprazole was also superior to placebo as maintenance therapy. Hospitalization risk was lower for quetiapine than for olanzapine or risperidone in a retrospective database study. Aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone monotherapies all have been shown to be superior to placebo on efficacy outcomes for acute mania. As add-on therapy, olanzapine, quetiapine, and risperidone, but not ziprasidone, were also superior to placebo on those same outcome measures. Compared with placebo, rates of symptom remission were consistently higher for olanzapine and quetiapine when added to lithium or valproate/divalproex and higher for quetiapine and risperidone when used as monotherapy. In head-to-head trials, olanzapine and quetiapine did not differ from risperidone in primary efficacy outcomes.

Quetiapine and olanzapine were the only AAPs shown to be superior to placebo in reducing depressive symptoms in adult patients with predominantly bipolar I depression. In a post hoc analysis, 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 symptoms were found for the intramuscular (IM) forms of aripiprazole and olanzapine compared with IM lorazepam and IM haloperidol, respectively. The only evidence about use of AAPs in adult patients with rapid cycling bipolar disorder comes from subgroup analyses. When the most recent episode was manic or mixed greater improvement was seen with aripiprazole and olanzapine than placebo. Clozapine was no better than chlorpromazine as acute monotherapy over three weeks in inpatients with manic or mixed episodes. No trials of paliperidone in patients with bipolar disorder were found.

Short-term harms from bipolar disease studies are summarized in Table 3.

Table 3

Harm Outcomes	Findings
Overall AE	Quetiapine worse than risperidone
Weight Gain	Compared with placebo, weight gain was greater with olanzapine, quetiapine, and risperidone, but not with aripiprazole or ziprasidone.
Prolactin (serum)/ Sexual Dysfunction	Increased with risperidone compared with olanzapine
EPS	Greater than placebo for aripiprazole, ziprasidone, risperidone
Diabetes Mellitus	Compared with CAPs, increased risk for clozapine, risperidone, olanzapine, quetiapine, but not ziprasidone

Question #1a. For adults experiencing a first episode of schizophrenia, do the AAPs differ in benefits (efficacy, effectiveness) or harms?

Three small open-label trials compared olanzapine and risperidone in treating symptoms in patients with a first episode of psychosis suggestive of schizophrenia and related disorders. Results indicate no significant differences between the drugs in symptom response at six weeks, three months or four months.

Question #1b. For adult patients with schizophrenia, related psychoses (including first episode), bipolar mania or bipolar depression, what is the comparative evidence that differences in adherence or persistence among the AAPs correlates with a difference in clinical outcomes?

Only one study was designed to assess the correlation between adherence levels and outcomes. This study defined adherence as a medication possession ratio of >85% combined with a patient statement of compliance. Nonadherent patients were found to have higher rates of psychiatric hospitalizations, use of emergency psychiatric services, arrests, violence, victimizations, poorer mental functioning, poorer life satisfaction, greater substance use, and more alcohol-related problems.

Question #2: For children and adolescents with pervasive developmental disorders or DBDs, do the AAPs differ in benefits (efficacy, effectiveness) or harms?

The quality of the comparative evidence in children and adolescents is poor. No head-to-head trials have been reported and no effectiveness trials exist. In children with autism and other pervasive developmental disorders, risperidone (five trials) and olanzapine (one trial) were superior to placebo for improving behavioral symptoms. Olanzapine was similar in efficacy to haloperidol in one small study. Quetiapine for children with autism or DBDs 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 AAPs in this population.

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 three trials and greater with olanzapine than haloperidol in one trial. In a Cochrane meta-analysis of two trials of risperidone in children with autism, the mean difference in weight gain for risperidone compared with placebo was 1.78 kg. The incidence of EPSs and other AEs was low in short-term trials. For longer-term safety, no comparative evidence exists; only risperidone has been studied. Limited evidence reported weight gain ranged from 2.1 kg to 8.1 kg over one to two years. Other AEs were infrequent.

Question #3: For older adults with behavioral and psychological symptoms of dementia, do the AAPs differ in benefits (efficacy, effectiveness) or harms?

Seven head-to-head trials compared one AAP 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 (Clinical Antipsychotic Trials of Intervention Effectiveness) trial (CATIE-AD), which found similar rates of withdrawals and responses for olanzapine, risperidone, and quetiapine. One fair-quality study found no difference between olanzapine and risperidone or between these drugs and placebo on a variety of scales after ten weeks, while another 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, AEs, or death compared with placebo, but there was no difference between treatment groups for overall withdrawals. Other short-term head-to-head trials

found similar rates of withdrawals and AEs for olanzapine and risperidone, and for quetiapine and risperidone. Table IV below summarizes serious harms reported in included trials.

Table 4

Harm Outcomes	Findings
Mortality	Increased risk with risperidone vs. clozapine in schizophrenic patients Increased risk with olanzapine vs. clozapine, risperidone, CAP in elderly Increased risk with all AAPs in elderly with dementia
Cerebrovascular Events	Increased risk of stroke with olanzapine, risperidone in elderly with dementia (not supported by observational studies)
Diabetes Mellitus	Increased risk with olanzapine vs. risperidone (3 of 5 trials), risk greatest in women, early in treatment. No increased risk with clozapine vs. CAP.
Weight Gain	Weight gain 1-3 kg greater with olanzapine vs. risperidone Risk of >7% of body weight gain greater with olanzapine vs. risperidone
Neuroleptic Malignant Syndrome	No comparative studies found
Seizures	Seizure rates over 2 years for clozapine = 2.9% to 4.2% (2 studies)
Tardive Dyskinesia	Clozapine rates = 1% to 7% over 6-26 months Risperidone rates = 0% to 5% over 6-26 months (greater than olanzapine) Olanzapine rate = 1% at 6 months (no difference compared with quetiapine)
Myocarditis/ Cardiomyopathy	Increased risk of myocarditis/cardiomyopathy with clozapine (not olanzapine, quetiapine, risperidone), lower risk with aripiprazole Increased risk cardiac arrest with risperidone vs. clozapine Increased risk of hypertension with ziprasidone
Agranulocytosis	Incidence with clozapine over 2-5 years = 0% to 5.9% (7 studies)

### Conclusion:

In schizophrenia, clozapine is superior to olanzapine in preventing suicidality and has lower rates of weight gain. Risk of relapse is lower with olanzapine than quetiapine and possibly risperidone. There is likely a lower risk of hospitalization with olanzapine compared to quetiapine, risperidone, and ziprasidone, although observational study results were conflicting. Good-quality evidence did not differentiate olanzapine, quetiapine, risperidone, or ziprasidone in QOL measures, although improvements were seen with all the drugs. Both clozapine and olanzapine have lower drug discontinuation rates than aripiprazole, quetiapine, risperidone and ziprasidone. Consistent differences in *efficacy* were not found between clozapine, olanzapine, quetiapine, risperidone, ziprasidone, or aripiprazole in shorter-term trials of inpatients or outpatients. Olanzapine is the most well studied AAP as maintenance therapy for bipolar disorder and was superior to placebo and comparable to lithium and divalproex in preventing relapse. Aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone monotherapies all have been shown to be superior to placebo on efficacy outcomes for acute mania. Quetiapine and olanzapine are the only AAPs shown to be superior to placebo in reducing depressive symptoms in patients with predominantly bipolar I depression. In children with autism and other pervasive developmental disorders, risperidone and olanzapine were superior to placebo for improving behavioral symptoms. In children and adolescents with DBDs, risperidone is superior to placebo. For patients with behavioral and psychological symptoms of dementia, the CATIE-AD trial found similar rates of withdrawals and response for olanzapine, risperidone, and quetiapine. Rates and severity of EPS were not found to be different among the drugs in most trials. Weight gain in clinical trials was greater with olanzapine than the other AAPs, as was the incidence of diabetes.