Comparative Effectiveness Review
Number 43

Effective Health Care Program

Off-Label Use of Atypical Antipsychotics: An Update

Executive Summary

Background

Antipsychotics medications are approved by the U.S. Food and Drug Administration (FDA) for treatment of schizophrenia and bipolar disorder. These medications are commonly divided into two classes, reflecting two waves of historical development: the conventional antipsychotics and the atypical. The conventional antipsychotics served as the first successful pharmacologic treatment for primary psychotic disorders such as schizophrenia. Having been widely used for decades, the conventional antipsychotics also produced various side effects requiring additional medications, which spurred the development of the atypical antipsychotics.

Currently, nine atypical antipsychotic drugs have been approved by FDA: aripiprazole, asenapine, clozapine, iloperidone, olanzapine, paliperidone, quetiapine, risperidone, and ziprasidone. These drugs have been used off-label (i.e., for indications not approved by FDA) for the treatment of various psychiatric conditions. While it is legal for a physician to prescribe drugs in such a manner, it is illegal for the manufacturer to actively promote such use.

A 2006 study on Efficacy and Comparative Effectiveness of Off-label Use of Atypical Antipsychotics reviewed the scientific evidence on the safety, efficacy, and effectiveness for off-label uses. (Clozapine was excluded because of its association with a potentially fatal blood disorder of bone marrow suppression, and it requires frequent blood tests for safety monitoring.) The 2006 study examined 84 published studies on atypicals and found that the

Effective Health Care Program

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.**

AHRQ Agency for Healthcare Research and Quality
Advancing Excellence in Health Care • www.ahrq.gov

Effective Health Care

most common off-label uses of the drugs were for treatment of depression, obsessive-compulsive disorder (OCD), post-traumatic stress disorder (PTSD), personality disorders, Tourette's syndrome, autism, and agitation in dementia. It concluded that with few exceptions, there was insufficient high-strength evidence to reach conclusions about the efficacy of any off-label uses of these medications. It also found strong evidence that atypicals are associated with increased risk of adverse events such as significant weight gain, sedation, and, among the elderly, increased mortality. Future research areas suggested by the report include safe treatment for agitation in dementia, association between the increased risk of death and antipsychotics drugs, and comparison of the development of adverse effects between patients taking atypical antipsychotics and those taking conventional antipsychotics.

Since publication of that report, important changes have occurred that make the report out of date. Studies have been published on new off-label uses, such as treatment of eating disorders, insomnia, attention-deficit hyperactivity disorder (ADHD), anxiety, and substance abuse. New or increased adverse effects of off-label indications have been observed and new atypicals (asenapine, iloperidone, and paliperidone) have been approved by FDA for the treatment of schizophrenia and bipolar disorder. In addition, the following previously off-label uses have been approved for on-label use by the FDA:

- Quetiapine and quetiapine ER (extended release) as monotherapy in bipolar depression
- Quetiapine ER as augmentation for major depressive disorder (MDD)
- Aripiprazole as augmentation for MDD
- Olanzapine/fluoxetine combination for MDD
- Olanzapine/fluoxetine combination for bipolar depression
- Risperidone and aripiprazole for autism spectrum disorders

An update is needed to better understand the trends in off-label use and the associated risks and benefits. Further, a number of issues remain unclear due to insufficient information in the previous report: subpopulations (i.e., race/ethnicity, gender) that would benefit most from atypical antipsychotics, appropriate dose, and time needed to see clinical improvement. This update will try to address these issues.

This report covers the following off-label uses of atypical antipsychotic medications: anxiety, ADHD, dementia and severe geriatric agitation, major depressive disorder (MDD), eating disorders, insomnia, OCD, PTSD, personality disorders, substance abuse, and Tourette's syndrome. Autism, included in the original systematic review, is now reviewed in a study on the comparative effectiveness of typical and atypical antipsychotics for on-label indications, conducted by another organization.

This report addresses the following Key Questions:

Key Question 1: What are the leading off-label uses of atypical antipsychotics in utilization studies? How have trends in utilization changed in recent years, including inpatient versus outpatient use? What new uses are being studied in trials?

Key Question 2: What does the evidence show regarding the efficacy and comparative effectiveness of atypical antipsychotics for off-label indications?

Sub-Key Question 2: How do atypical antipsychotic medications compare with other drugs, including first-generation antipsychotics, for treating off-label indications?

Key Question 3: What subset of the population would potentially benefit from off-label uses? Do effectiveness and harms differ by race/ethnicity, gender, and age group? By severity of condition and clinical subtype?

Key Question 4: What are the potential adverse effects and/or complications involved with off-label prescribing of atypical antipsychotics? How do they compare within the class and with other drugs used for the conditions?

Key Question 5: What is the effective dose and time limit for off-label indications?

Conclusions

Key Question 1: What are the leading off-label uses of atypical antipsychotics in utilization studies? How have trends in utilization changed in recent years, including inpatient versus outpatient use? What new uses are being studied in trials?

Atypicals have been studied as off-label treatment for the following conditions: ADHD, anxiety, dementia in elderly patients, depression, eating disorders, insomnia, OCD, personality disorder, PTSD, substance use disorders, and Tourette's syndrome.

Off-label use of atypical antipsychotics in various settings has increased rapidly since their introduction in the 1990s; risperidone, quetiapine, and olanzapine are the most common atypicals prescribed for off-label use.

One recent study indicated that the 2005 regulatory warning from the FDA and Health Canada was associated with decreases in the overall use of atypical antipsychotics, especially among elderly dementia patients.

Use of atypicals in the elderly is much higher in long-term care settings than in the community.

Atypicals are frequently prescribed to treat PTSD in the U.S. Department of Veterans Affairs health system.

At least 90 percent of antipsychotics prescribed to children are atypical, rather than conventional antipsychotics. The majority of use is off-label.

No off-label use of the newly approved atypicals (asenapine, iloperidone, and paliperidone) was reported in the utilization literature.

Key Question 2: What does the evidence show regarding the efficacy and comparative effectiveness of atypical antipsychotics, for off-label indications? Sub-Key Question 2: How do atypical antipsychotic medications compare with other drugs, including first-generation antipsychotics, for treating off-label indications?

The efficacy results are summarized in Table A below. It is important to note that no trials of the three most recently FDA-approved atypicals (asenapine, iloperidone, and paliperidone) were found for off-label use. Cells shaded in dark blue indicate areas with the strongest evidence of efficacy, followed by the areas in orange. Areas containing circles indicate areas where no clinical trials exist. Light orange and light blue areas indicate areas where evidence of inefficacy exists. Areas in medium blue indicate mixed results.

Table A. Summary of strength of evidence of efficacy, by drug and condition

	Aripiprazole	Olanzapine	Quetiapine	Risperidone	Ziprasidone
Anxiety					
- generalized anxiety disorder	O	-	++	-	-
Anxiety					
- social phobia	O	+	-	O	O
Attention Deficit/Hyperactivity Disorder					
-no co-occurring disorders	O	O	O	+	O
Attention Deficit/Hyperactivity Disorder					
-bipolar children	-	O	O	O	O
Attention Deficit/Hyperactivity Disorder					
-mentally retarded children	O	O	O	+	O
Dementia overall	++	+	+	++	O
Dementia psychosis	+	+-	+-	++	O
Dementia agitation	+	++	+-	++	O
Depression					
-MDD augmentation of SSRI/SNRI	++	+	++	++	+
Depression					
-MDD: Monotherapy	O	-	++	O	O
Eating Disorders	O	--	-	O	O
Insomnia	O	O	-	O	O
Obsessive Compulsive Disorder					
-augmentation of SSRI	O	+	--	++	-
Obsessive Compulsive Disorder					
-augmentation of citalopram	O	O	+	+	O
Personality Disorder					
-borderline	+	+-	+	O	-

Table A. Summary of strength of evidence of efficacy, by drug and condition (continued)

	Aripiprazole	Olanzapine	Quetiapine	Risperidone	Ziprasidone
Personality Disorder					
-schizotypal	O	O	O	+-	O
Post Traumatic Stress Disorder	O	+-	+	++	O
Substance Abuse alcohol	--	-	-	O	O
Substance Abuse cocaine	O	-	O	-	O
Substance Abuse methamphetamine	-	O	O	O	O
Substance Abuse methadone clients	O	O	O	-	O
Tourette's Syndrome	O	O	O	+	-

++: moderate or high evidence of efficacy
+ : low or very low evidence of efficacy
+- : mixed results
- : low or very low evidence of inefficacy
-- : moderate or high evidence of inefficacy
O : no trials
□: Approved by FDA for the indication

MDD = major depressive disorder; SSRI = selective serotonin reuptake inhibitor; SNRI = serotonin-norepinephrine reuptake inhibitors

Note: Symbols denote strength of evidence, not size of portential effect. For example, in dementia "++" indicates moderate-to-high strength of evidence that there is a beneficial effect; however, the size of the effect is small.

Table B below shows how our current efficacy findings compare with those of our original Comparative Effectiveness Review (CER) submitted to the Agency for Healthcare Research and Quality (AHRQ) in 2006. The evidence that atypicals have efficacy in treating symptoms of dementia has increased in the past few years; this evidence must be weighed against possible harms described in Key Question 4 below. Evidence of efficacy as augmentation for MDD and OCD patients who have not responded adequately to selective serotonin reuptake inhibitors/serotonin-norepinephrine reuptake inhibitors (SSRIs/SNRIs) has also increased. Table B is organized as follows: First, all conditions dealt with in our original CER, in alphabetical order; second, all the new off-label indications in alphabetical order.

Key Question 3: What subset of the population would potentially benefit from off-label uses? Do effectiveness and harms differ by race/ethnicity, gender, and age group? By severity of condition and clinical subtype?

There are insufficient data regarding efficacy, effectiveness, and harms to determine what subset of the population would potentially benefit from off-label uses of atypicals. Only one study conducted a subgroup analysis by gender; there were no studies that stratified by racial or ethnic group. Although many studies specified age in their inclusion criteria, few studies stratified results by age.

Examination of the literature for differing efficacy of atypicals by clinical subsets did not reveal studies reporting subgroup analyses. Our own meta-analysis found efficacy for combat-related PTSD in men but not for PTSD in civilian women, although these data come from separate literatures, and head-to-head comparison of gender effects within study have not been performed. Due to the varying measures utilized in determining severity of illness, it was not possible to analyze treatment effects by severity of illness across any other condition.

Key Question 4: What are the potential adverse effects and/or complications involved with off-label prescribing of atypical antipsychotics? How do they compare within the class and with other drugs used for the conditions?

Table C compares the most important findings regarding adverse events, by age group and study design.

Table B. Summary update: efficacy of atypical antipsychotics for off-label use				
Usage	**Strength of Evidence**	**2006 Findings**	**2011 Findings**	**2011 Conclusions**
Dementia	High	A published meta-analysis of 15 placebo-controlled trials (PCTs) found small but statistically significant effects favoring treatment with risperidone and aripiprazole. There were effects that favored treatment with olanzapine for the BPRS and the NPI, but these differences were not statistically significant. 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.	Overall – In our meta-analysis of PCTs, aripiprazole, olanzapine, and risperidone were superior to placebo as treatment of behavioral symptoms as measured by total scores on BEHAVE-AD, BPRS, and NPI. Effect sizes were generally considered to be "small" in magnitude. Psychosis – In our meta-analysis risperidone was superior to placebo, as measured by the psychosis subscales of the BEHAVE-AD, BPRS, and NPI. Results for aripiprazole did not meet conventional levels of statistical significance. Agitation – In our meta-analysis, aripiprazole, olanzapine and risperidone were superior to placebo, as measured by the agitation subscales of the BEHAVE-AD, BPRS, NPI, and CMAI. Three head to head trials compared atypicals; none was found superior.	Aripiprazole, olanzapine, and risperidone **have efficacy** as treatment for behavioral symptoms of dementia.

Table B. Summary update: efficacy of atypical antipsychotics for off-label use (continued)				
Usage	**Strength of Evidence**	**2006 Findings**	**2011 Findings**	**2011 Conclusions**
Depression – MDD: augmentation of SSRI/SNRI	Moderate – risperidone, aripiprazole, quetiapine Low – olanzapine, ziprasidone	Three trials assessed the combination of olanzapine and fluoxetine, one trial each assessed augmentation of various SRIs with risperidone, ziprasidone, and quetiapine, and one study assessed adding risperidone versus olanzapine to SSRI. 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. The one trial that directly compared augmentation therapy between olanzapine and risperidone reported no differences in outcome.	We conducted a meta-analysis using "response" to treatment and remission as outcome. Pooling trials that reported the HAM-D as outcome, the relative risk of responding for participants taking quetiapine or risperidone was significantly higher than for placebo. Olanzapine had only two trials, so pooling was not performed; the trials reported olanzapine superior to placebo. Other trials reported MADRS scores; the relative risk of responding for participants taking aripiprazole was significantly higher than those taking placebo. Risperidone and ziprasidone were included in two trials and one trial, respectively. These reported the drug superior to placebo. One trial compared ziprasidone at differing levels augmenting sertraline to sertraline alone. This trial found a greater improvement in CGI-S and MADRS scores augmenting with ziprasidone at 160mg than either augmentation with ziprasidone at 80mg or sertraline alone. However, there was no significant difference in HAMD-17, CGI-I or HAM-A scores.	Aripiprazole, quetiapine, and risperidone **have efficacy** as augmentation to SSRIs/SNRIs for major depressive disorder. Olanzapine and ziprasidone **may also have efficacy**.
Depression – MDD: Monotherapy	Moderate	The three olanzapine studies (above) also assessed its efficacy as monotherapy. Olanzapine alone was no better than placebo in improving symptoms at 6 or 12 weeks. Outcomes were too heterogeneous to allow pooling.	In our meta-analysis of five placebo-controlled trials, quetiapine was superior according to relative risk of both responding and remitted as measured by MADRS.	Olanzapine **does not have efficacy** as monotherapy for major depressive disorder. Quetiapine **has efficacy** as monotherapy for major depressive disorder.

Table B. Summary update: efficacy of atypical antipsychotics for off-label use (continued)				
Usage	**Strength of Evidence**	**2006 Findings**	**2011 Findings**	**2011 Conclusions**
Obsessive-compulsive disorder – augmentation of SSRI	Moderate –risperidone Low – olanzapine	Twelve trials used risperidone, olanzapine, or quetiapine as augmentation therapy in patients who were resistant to treatment with SSRI. Nine trials were sufficiently similar clinically to pool. Atypical antipsychotics had a clinically important benefit (measured by the Yale-Brown Obsessive-Compulsive Scale) when used as augmentation therapy. Relative risk of "responding" significant for augmentation with quetiapine and risperidone. There were too few studies of olanzapine augmentation to permit separate pooling of this drug.	Our updated meta-analysis found risperidone superior to placebo, as measured by changed in the Yale Brown Obsessive Compulsive Scale (Y-BOCS). There were too few studies (two) to permit separate pooling for olanzapine; both trials reported olanzapine superior to placebo. One new head to head trial found no difference in effect between olanzapine and risperidone as SSRI augmentation. One new head to head trial found quetiapine more effective than ziprasidone as SSRI augmentation. One new trial compared quetiapine to clomipramine as SSRI augmentation. Quetiapine produced a significant reduction in Y-BOCS score, while clomipramine did not.	Risperidone **has efficacy** in improving OCD symptoms when used as an adjunct to SSRI in treatment refractory patients. Olanzapine may also **have efficacy**. Quetiapine is more **efficacious** than ziprasidone and clomipramine for this purpose.
Obsessive-compulsive disorder – augmentation of citalopram	Low–quetiapine Very low – risperidone	One trial of risperidone reported no differences between groups in achieving a response to therapy, but patients maintained on risperidone had a significantly longer period of time to relapse compared to placebo (102 days vs. 85 days)	Two new trials found quetiapine superior to placebo as augmentation for citalopram, according to Y-BOCS and CGI-I scores.	Quetiapine and risperidone may be **efficacious** as augmentation to citalopram in OCD patients.
Post-traumatic stress disorder	Moderate – risperidone Olanzapine – Low Quetiapine – very low	Four trials of risperidone and two trials of olanzapine, each of at least 6 week duration, treated patients with PTSD. Three trials enrolled 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. Three trials of olanzapine or risperidone as monotherapy for abused women with PTSD were inconclusive regarding efficacy.	Three new trials of risperidone were found, allowing us to conduct a meta-analysis using the Clinician Administered PTSD Scale (CAPS) as outcome. Risperidone was superior to placebo. There were too few olanzapine studies (two) to pool; one reported olanzapine superior to placebo, while one did not. A new trial found a 3-fold decline in CAPS scores in patients treated with quetiapine monotherapy compared to placebo. Exact scores were not reported. We also conducted a meta-analysis by condition; atypicals were efficacious for combat-related PTSD but not PTSD in abused women.	Risperidone is **efficacious** in reducing combat-related PTSD symptoms when used as an adjunct to primary medication.

Table B. Summary update: efficacy of atypical antipsychotics for off-label use (continued)				
Usage	**Strength of Evidence**	**2006 Findings**	**2011 Findings**	**2011 Conclusions**
Personality disorders – borderline	Low – aripiprazole Very low – quetiapine, olanzapine	Three trials provide evidence that olanzapine is superior to placebo and may be superior to fluoxetine. The benefit of adding olanzapine to dialectical therapy in one trial was small. Aripiprazole was superior to placebo in one small trial.	One new trial found aripiprazole superior to placebo in improving SCL-90, HAM-D, and HAM-A scores at 8 months and less self-injury at 18 months. One new trial of ziprasidone found no significant difference in CGI-BPD, depressive, anxiety, psychotic or impulsive symptoms compared to placebo at 12 weeks. Two new trials of olanzapine found no difference from placebo in any outcomes, while another new trial of olanzapine found greater change in ZAN-BPD scores at 12 weeks, compared with placebo. One new trial found quetiapine superior to placebo on BPRS, PANSS scales. Due to heterogeneity of outcomes, we could not perform a meta-analysis.	Olanzapine had **mixed results** in 7 trials, aripiprazole was found **efficacious** in two trials, quetiapine was found **efficacious** in one trial, and ziprasidone was found **not efficacious** in one trial.
Personality disorders – schizotypal	Low	Risperidone was superior to placebo in one small trial.	One new small trial of risperidone found no difference from placebo on a cognitive assessment battery.	Risperidone had **mixed results** when used to treat schizotypal personality disorder in two small trials.
Tourette's syndrome	Low	Risperidone was superior to 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 other trials. One trial of ziprasidone showed variable efficacy compared to placebo.	No additional trials.	Same as 2006: Risperidone **is at least as efficacious as pimozide or clonidine** for Tourette's syndrome.
Anxiety	Moderate	Not covered.	Three placebo-controlled trials of quetiapine as monotherapy for Generalized Anxiety Disorder (GAD) could be pooled; relative risk of responding on HAM-A favored the quetiapine group. One head to head trial showed no difference between risperidone and paroxetine on HAM-A score improvement. One trial each found quetiapine equally effective as paroxetine and escitalopram.	Quetiapine **has efficacy** as treatment for Generalized Anxiety Disorder

Table B. Summary update: efficacy of atypical antipsychotics for off-label use (continued)				
Usage	**Strength of Evidence**	**2006 Findings**	**2011 Findings**	**2011 Conclusions**
Attention deficit/ hyperactivity disorder – no co-occurring disorders	Low	Not covered.	One trial showed risperidone superior to placebo in reducing scores on the Children's Aggression Scale – Parent version (CAS-P).	Risperidone may be **efficacious** in treating children with ADHD with no serious co-occurring disorders.
Attention deficit/ hyperactivity disorder–mentall y retarded children	Low	Not covered.	One trial showed risperidone led to greater reduction in SNAP-IV (Swanson, Nolan, and Pelham teacher & parent rating scale) scores than methylphenidate.	Risperidone **may be superior to methylphenidate** in treating ADHD symptoms in mentally retarded children.
Attention deficit/ hyperactivity disorder – bipolar children	Low	Not covered.	Two trials of aripiprazole showed no effect on SNAP-IV (Swanson, Nolan, and Pelham teacher & parent rating scale) scores than placebo.	Aripiprazole is **inefficacious** in reducing ADHD symptoms in children with bipolar disorder.
Eating disorders	Moderate – olanzapine Low - quetiapine	Not covered.	Five trials of olanzapine were found; three reporting Body Mass Index (BMI) could be pooled. There was no difference in change in BMI at either one or three months compared to placebo. One trial of quetiapine reported no statistical difference from placebo in BMI increase at three months.	Olanzapine and quetiapine **have no efficacy** in increasing body mass in eating disorder patients.
Insomnia	Very low.	Not covered.	In one small trial (N=13) of quetiapine, sleep outcomes were not statistically different from placebo.	Quetiapine may be **inefficacious** in treating insomnia.
Substance abuse – alcohol	Moderate – aripiprazole Low – quetiapine	Not covered. Not covered.	Two trials of aripiprazole and one of quetiapine reported % of patients completely abstinent during follow-up. In our pooled analysis, the effect versus placebo was insignificant.	Aripiprazole is **inefficacious** in treating alcohol abuse /dependence. Quetiapine may also be **inefficacious**.

Table B. Summary update: efficacy of atypical antipsychotics for off-label use (continued)				
Usage	**Strength of Evidence**	**2006 Findings**	**2011 Findings**	**2011 Conclusions**
Substance abuse – cocaine	Low	Not covered.	Two trials of olanzapine and one of risperidone reported there was no difference in efficacy versus placebo as measured by the Addiction Severity Index (ASI).	Olanzapine is **inefficacious** in treating cocaine abuse/ dependence. Risperidone may also be **inefficacious**.
Substance abuse – meth-amphetamine	Low	Not covered.	One trial found aripiprazole inefficacious in reducing use of intravenous amphetamine, as measured by urinalysis. Another trial found aripiprazole inefficacious in reducing craving for methamphetamine.	Aripiprazole is **inefficacious** in treating methamphetamine abuse/dependence.
Substance abuse – methadone clients	Low	Not covered.	One trial of methadone clients found no difference between risperidone and placebo in reduction of cocaine or heroin use.	Risperidone is an inefficacious adjunct to methadone maintenance.

ADHD = attention-deficit hyperactivity disorder; BEHAVE-AD = Behavioral Pathology in Alzheimer's Disease Scale; BPRS = Brief Psychiatric Rating Scale; CGI-BPD = Clinical Global Impression Scale for Borderline Personality Disorder; CGI-I = Clinical Global Impression Improvement; CGI-S = Clinical Global Impression-Severity; CMAI = Cohen-Mansfield Agitation Inventory; HAM-A = Hamilton Anxiety Scale; HAM-D = Hamilton Depression Rating Scale; MADRS = Montgomery-Asberg Depression Rating Scale; MDD = major depressive disorder; NPI = Neuropsychiatric Inventory; OCD = obsessive-compulsive disorder; PANSS = Positive and Negative Syndrome Scale; PCT = placebo-controlled trial; PTSD = post-traumatic stress disorder; SSRI = selective serotonin reuptake inhibitor; SNRI = serotonin-norepinephrine reuptake inhibitors; ZAN-BPD = Zanarini Rating Scale for Borderline Personality Disorder

Table C. Summary update: safety of atypical antipsychotics for off-label use			
Adverse Event	**Head-to-Head Comparisons**	**Active Comparisons**	**Placebo Comparisons**
Weight gain– Elderly patients	In one large trial (CATIE-AD) patients who were treated with olanzapine, quetiapine, or risperidone averaged a monthly gain of 1.0, 0.7, and 0.4 lbs respectively, compared with a monthly weight loss of 0.9 lbs for placebo patients.	More common in patients taking olanzapine than risperidone or conventional antipsychotics, particularly if their BMI was less than 25 at baseline, according to a large cohort study.	More common in patients taking olanzapine and risperidone than placebo according to our meta-analysis.
Weight gain– Adults 18–64	More common in olanzapine patients than ziprasidone patients in one trial.	More common among patients taking olanzapine than patients taking conventional antipsychotics in three trials. More common in patients taking aripiprazole than patients taking conventional antipsychotics in one trial. More common among patients taking olanzapine than patients taking mood stabilizers in two trials.	More common in patients taking aripiprazole, olanzapine, quetiapine, and risperidone than placebo according to our meta-analysis.
Weight gain– Children & adolescents	No head-to-head studies.	No difference between clonidine and risperidone in one trial.	More common in patients taking risperidone in two PCTs. No difference in one small PCT of ziprasidone.
Mortality– Elderly patients	No difference between olanzapine and risperidone according to a meta-analysis of six trials of olanzapine published in 2006.	Six large cohort studies compared mortality in elderly patients taking atypical and conventional antipsychotics. Four of these studies found a significantly higher rate of death with conventional antipsychotics, while two found no statistical difference in mortality between the drug classes.	The difference in risk for death was small but statistically significant for atypicals, according to a 2006 meta-analysis which remains the best available estimate. Sensitivity analyses found no difference between drugs in the class. Patients taking atypicals had higher odds of mortality than those taking no antipsychotics in the two cohort studies that made that comparison. There are no trials or large observational studies of ziprasidone in this population; therefore, we cannot make conclusions regarding safety here.

Table C. Summary update: safety of atypical antipsychotics for off-label use (continued)			
Adverse Event	**Head-to-Head Comparisons**	**Active Comparisons**	**Placebo Comparisons**
Endocrine/ diabetes – Elderly patients	No evidence reported.	No evidence reported.	No difference in endocrine events in risperidone patients in one PCT. Regarding diabetes, risk was elevated but not statistically significant in one industry-sponsored cohort study of olanzapine patients.
Endocrine/ diabetes – Adults 18–64	Diabetes more common in patients taking olanzapine than patients taking risperidone in one trial.	No evidence reported.	Endocrine events more common in patients taking quetiapine, risperidone, and ziprasidone in one PCT each. More common in olanzapine in two pooled PCTs. Diabetes more common in patients taking quetiapine in six pooled PCTs; however, the pooled odds ratio was elevated at 1.47 but not statistically significant. More common in olanzapine patients in one PCT; the odds ratio of 5.14 was not statistically significant, with very wide confidence intervals (0.6 to 244). Lower odds of diabetes in risperidone patients in one large observational study

Table C. Summary update: safety of atypical antipsychotics for off-label use (continued)			
Adverse Event	**Head-to-Head Comparisons**	**Active Comparisons**	**Placebo Comparisons**
CVA – Elderly patients	No evidence reported.	Hospitalization for CVA was increased in the first week after initiation of conventional antipsychotics, but not for initiation of atypicals in a large cohort study.	More common in risperidone patients than placebo according to four PCTs pooled by the manufacturer. In our new meta-analysis of PCTs, risperidone was the only drug associated with an increase. More common in olanzapine than placebo according to five PCTs pooled by the manufacturer.
EPS –	More common in patients taking aripiprazole and risperidone patients than patients taking quetiapine in one large trial (CATIE-AD).	No evidence reported.	More common in patients taking risperidone, according to our meta-analysis. Quetiapine and aripiprazole were not associated with an increase. More common in olanzapine in one PCT.
EPS – Adults 18–64	No evidence reported.	Less likely in patients taking quetiapine than mood stabilizers in one small trial. Less likely in patients taking olanzapine or aripiprazole than patients taking conventional antipsychotics in one trial each.	More common in patients taking aripiprazole, quetiapine, and ziprasidone than placebo according to our meta-analysis.
Sedation – Elderly patients	More common in elderly patients taking olanzapine or quetiapine than risperidone according to our analysis, but not quite statistically significant.	No difference in one trial of olanzapine versus benzodiazepines. No difference in three trials of olanzapine and three of risperidone versus conventional antipsychotics.	More common in patients taking aripiprazole, olanzapine, quetiapine, and risperidone than placebo according to our meta-analysis.
Sedation – Children and adolescents	No head-to-head trials.	No difference in one small trial of clonidine versus risperidone. More patients on haloperidol than risperidone reported sleep problems in one trial.	Less common in aripiprazole patients than placebo patients in one PCT. No difference from placebo in one small PCT of ziprasidone.

Table C. Summary update: safety of atypical antipsychotics for off-label use (continued)			
Adverse Event	**Head-to-Head Comparisons**	**Active Comparisons**	**Placebo Comparisons**
Sedation – Adults 18–64	More common in patients taking quetiapine than risperidone in two trials.	Olanzapine patients had higher odds than mood stabilizer patients in two trials. No difference in one trial of risperidone versus olanzapine. More common in olanzapine and quetiapine patients than SSRIs patients in three and two trials respectively. Olanzapine patients had lower odds than patients taking conventional antipsychotics in our pooled analysis of three trials.	More common in patients taking aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone than placebo in our meta-analysis.

BMI = body mass index; CATIE-AD = Clinical Antipsychotic Trials of Intervention Effectiveness-Alzheimer's Disease; CVA = cerebrovascular accident; EPS = extrapyramidal symptoms; PCT = placebo-controlled trial; SSRI = serotonin selective reuptake inhibitor

Key Question 5: What is the effective dose and time limit for off-label indications?

There are too few studies comparing doses of atypical antipsychotic medications to draw a conclusion about a minimum dose needed. Most trials used flexible dosing, resulting in patients taking a wide range of doses. According to a meta-analysis we were able to conduct using the percentage of remitters and responders according to the MADRS as outcome, 150 mg quetiapine daily augmentation has equal efficacy as augmentation with 300 mg for patients with MDD who respond inadequately to SSRIs. More trials examining different doses of other atypicals for MDD would help guide clinicians in treating this population. In addition, more dosage trials for treating conditions such as OCD, PTSD, and anxiety disorder would allow for pooling and comparison of results.

Though there is some trial data regarding duration of treatment in PTSD, eating disorders, and borderline personality disorder, the outcome of treatment appears to be the same regardless of reported followup time.

Remaining Issues

The overarching finding of this review is that although atypical antipsychotic medications are used for a large number of off-label indications, there is moderate to strong evidence of efficacy for only a few of the drugs and for only a few of the off-label indications. Most of the evidence is for the drugs risperidone, olanzapine, and quetiapine, for the off-label indications of dementia, depression, and OCD. For the newly approved atypicals (asenapine, iloperidone, and paliperidone), we found no clinical trials assessing their use for any off-label condition, and for some off-label uses, we found no or only a small number of trials. Head-to-head comparisons of atypical antipsychotic drugs for off-label uses are few, and evidence from placebo-controlled trials for off-label use suggests that efficacy differs between drugs, meaning that the assumption of a "class effect" for atypical antipsychotics may be unwarranted. This means that each drug requires its own evaluation of efficacy for each off-label indication, which is a large task; drugs demonstrated to be efficacious will need to be compared in head-to-head in trials.

There is almost no evidence about how treatment efficacy may vary within populations, including variations due to gender, race, ethnicity, or medical comorbidities. In addition, existing evidence about the role of baseline severity of disease is too heterogeneous to allow us to draw conclusions. In future research, standardized measures of disease severity might allow for greater knowledge of the patient populations who would benefit from treatment with atypical agents.

Regarding adverse effects of the atypical antipsychotics, existing evidence varies by drug and by description of the adverse event. It would facilitate assessments of comparative effectiveness if future studies contained a standardized list of assessed side effects. As many trials report only those side effects observed, we are unable to compare between trials for many of the side effects.

Another area where clinical guidance is needed is in the dosages required to achieve effects in off-label indications. The dosages used in off-label indications varied from those used in on-label indications. There were few trials that compared effects by dose. Most studies used "flexible" dosing, where a patients dosage can be adjusted during the trial. Thus, a dosage comparison across trials was generally not possible. More research, examining differing dosages within the same population, is required in order to guide clinicians in the appropriate doses to prescribe. A similar issue is that of treatment length. More research reporting responses at various time points would be helpful in determining how long treatment is required. Given the risk of side effects when using these agents, clinicians need to know when a result is expected to prevent continuing an inefficacious agent, unnecessarily.

Newer agents, such as asenapine, iloperidone, and paliperidone, cannot be assumed to have efficacy and harms similar to the older atypical antipsychotics, since the evidence to date does not support that there is a general "class effect" in terms of either efficacy or harm for most off-label indications. Trials assessing the newer agents' efficacy and safety are necessary if they are to be used off-label for any of the above treatment areas.

Full Report

This executive summary is part of the following document: Maglione M, Ruelaz Maher A, Hu J, Wang Z, Shanman R, Shekelle PG, Roth B, Hilton L, Suttorp MJ, Ewing BA, Motala A, Perry T. Off-Label Use of Atypical Antipsychotics: An Update. Comparative Effectiveness Review No. 43. (Prepared by the Southern California/RAND Evidence-based Practice Center under Contract No. HHSA290-2007-10062-1.) AHRQ Publication No. 11-EHC087-EF. Rockville, MD: Agency for Healthcare Research and Quality. September 2011. www.effectivehealthcare.ahrq.gov/reports/final.cfm.

For More Copies

For more copies of Off-Label Use of Atypical Antipsychotics: An Update: Executive Summary No. 43 (AHRQ Pub. No 11-EHC087-1), please call the AHRQ Clearinghouse at 1–800–358–9295 or email ahrqpubs@ahrq.gov.

AHRQ Pub. No. 11-EHC087-1
September 2011