

# Off-Label Use of Atypical Antipsychotics: An Update

## Focus of Research for Clinicians

In response to a request from the public regarding the expanding use of atypical antipsychotics to treat conditions other than approved indications, a review was undertaken to examine trends in use and to report what is known about the efficacy, comparative effectiveness, benefits, and adverse effects of atypical antipsychotics for “off-label” indications in adults. This summary is based on a systematic review that includes 170 studies of efficacy or comparative effectiveness and 180 studies reporting adverse effects. The literature search spanned all years available in the electronic databases through May 2011. Review findings about antipsychotic use in children are not included in this clinician research summary. The full report, listing all studies, is available at [www.effectivehealthcare.ahrq.gov/offlabelantipsych.cfm](http://www.effectivehealthcare.ahrq.gov/offlabelantipsych.cfm). This summary, based on the full report of research evidence, is provided to clinicians to inform discussions of options with patients and to assist in decisionmaking along with consideration of a patient’s values and preferences. Reviews of evidence should not be construed to represent clinical recommendations or guidelines.

## Background

Antipsychotics are commonly divided into two classes, based on their timeline of development, pharmacology, and adverse effects. The typical antipsychotics, also called conventional or first-generation antipsychotics, were the first successful pharmacologic treatments for psychotic disorders such as schizophrenia. The poorly tolerated and in some cases irreversible adverse effects of the typical antipsychotics spurred another phase of development that produced the second-generation or atypical antipsychotics. By 2001, 96 percent of antipsychotics prescribed to new users were of the atypical class.

The U.S. Food and Drug Administration (FDA) has approved antipsychotics of both classes for the treatment of schizophrenia and bipolar disorder. More recently some atypical antipsychotics have also been approved for indications in major depressive disorder (MDD) and autism spectrum disorders. Prescribing of the atypicals has expanded beyond the approved indications, but their effectiveness, benefits, and adverse effects in off-label uses are not well understood.

## Conclusion

Overall, a class effect of the atypical antipsychotics for each disorder cannot be assumed, and for most atypicals, adequate supporting evidence for either efficacy or comparative effectiveness is still lacking for many indications. The trade-offs between risks and benefits (especially in the elderly) should be considered before instituting drug therapy, and careful monitoring for adverse effects is warranted.

Atypical antipsychotics can improve behavioral symptoms of dementia. Several atypical antipsychotics have approved indications in treatment of MDD, and additional members of the class show evidence of efficacy. There is a growing evidence base for the efficacy of atypicals, individually, in obsessive-compulsive disorder (OCD), combat-related post-traumatic stress disorder (PTSD), and generalized anxiety disorder. The evidence for efficacy in borderline personality disorders is too limited to estimate benefit, and the evidence is insufficient for

treatment of Tourette’s syndrome in adults. Evidence is stronger that atypical antipsychotics do not increase body weight in anorexia nervosa (although weight gain is a common adverse effect in other patients) or reduce substance abuse. There is little evidence about optimal dosages and durations of treatment in off-label use.

The risk of death in elderly patients (65 and older) is increased by both atypical and typical antipsychotics. Other adverse effects of the atypicals include an increased risk of weight gain, which is more common and severe with olanzapine. The risks for endocrine and metabolic abnormalities, including diabetes, are less certain, though measurable. Sedative effects of the atypicals are seen in adults of all age groups. The possibility of urinary adverse effects in elderly patients has appeared in studies of the atypical antipsychotics.

## Clinical Bottom Line

### Trends in Off-Label Use

- Nine atypical antipsychotics have received FDA approval to date: aripiprazole (Abilify®), asenapine (Saphris®), clozapine\* (Clozaril®), iloperidone (Fanapt®), olanzapine (Zyprexa®), paliperidone (Invega®), quetiapine (Seroquel XR®), risperidone (Risperdal®), and ziprasidone (Geodon®).
- Risperidone, quetiapine, and olanzapine are the most commonly prescribed atypical antipsychotics for off-label indications.
- Off-label use of the three most recently approved atypicals (asenapine, iloperidone, and paliperidone) has not been reported in the literature. The most commonly studied drug is risperidone, followed by olanzapine and quetiapine, with aripiprazole and ziprasidone the least investigated.
- Since the FDA regulatory warning in 2005 about severe adverse effects in the elderly, the use of atypical antipsychotics for treating the elderly has declined.
- Off-label use of atypical antipsychotics is higher in long-term care settings than in the community.

\*Clozapine causes a potentially fatal disorder of bone marrow suppression; prescribing requires frequent blood tests for safety monitoring. Its off-label use was not examined in this review.

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**Clinical Bottom Line** (Continued)

**Table 1. Strength of Evidence for Efficacy of Atypical Antipsychotics for Off-Label Indications**

The table below summarizes what is known about whether the listed medications can improve the symptoms of a particular disorder, as determined in placebo-controlled trials. The clinical study evidence does not support a general class effect for either efficacy or adverse effects for most off-label indications.

☑ = the medication can improve symptoms; ☒ = the medication does not improve symptoms

INDICATION	Aripiprazole	Olanzapine	Quetiapine	Risperidone
Dementia	Overall <sup>a</sup> ☑ ●●○ Agitation ☑ ●○○ Psychosis ☑ ●○○	Overall ☑ ●○○ Agitation ☑ ●●○ Psychosis ☒ ●○○	Overall ☑ ●○○	Overall ☑ ●●● Agitation ☑ ●●● Psychosis ☑ ●●●
MDD (augmentation) <sup>b</sup>	Approved indication	Approved indication	Approved indication <sup>c</sup>	☑ ●●○ Remission NNT = 8 Response NNT = 7
MDD (monotherapy) <sup>d</sup>	No trials	☒ ●●○	☑ ●●○ Remission NNT = 13 Response NNT = 6	No trials
OCD (augmentation) <sup>e</sup>	No trials	☑ ●○○ <sup>f</sup>	No trials	☑ ●●○ Response NNT = 5
PTSD (adjunctive)	No trials	○○○	○○○	☑ ●●○ <sup>g</sup> (combat-related)
GAD	No trials	No trials	☑ ●●○ Response NNT = 8 <sup>h</sup>	No trials
BPD <sup>i</sup>	☑ ●○○	○○○	☑ ●○○	No trials
Anorexia Nervosa (body weight)	No trials	☒ ●●○	☒ ●○○	No trials
Substance Abuse (reduction in use)	☒ Alcohol ●●○ ☒ Methamphetamine ●○○	☒ Alcohol ●○○ ☒ Cocaine ●○○	☒ Alcohol ●○○	☒ Cocaine ●○○ ☒ Methadone ●○○

Ziprasidone: OCD ☒ ●○○; BPD ☒ ●○○; other indications: no trials.

NNT, NNH = the number of patients that must be treated in order to see benefit (NNT) or harm (NNH) in one patient more than found in the comparison group, calculated from the difference in risk between the groups. The smaller the NNT or NNH value, the greater the effect attributable to the treatment. BPD = borderline personality disorder; GAD = generalized anxiety disorder; MDD = major depressive disorder; OCD = obsessive-compulsive disorder; PTSD = post-traumatic stress disorder; 95% CI = 95-percent confidence interval, the range of statistically valid values for the result; *p* < 0.05 when the CI does not include 1.0.

<sup>a</sup>Overall = total/global scores, for each drug where listed.

<sup>b</sup>Augmentation of SSRIs (selective serotonin reuptake inhibitors) or SNRIs (serotonin-norepinephrine uptake inhibitors); remission is defined as a score less than 7 on the HAM-D 17 (Hamilton Depression Rating Scale) or less than 8 on the HAM-D 24 over two consecutive visits; and response is defined as at least a 50% reduction in the HAM-D score.

<sup>c</sup>Approved for use in combination with fluoxetine.

<sup>d</sup>No atypical antipsychotic has been approved for use as a monotherapy for MDD.

<sup>e</sup>Augmentation of SSRIs; response is defined as at least a 25–35% improvement in the YBOCS (Yale-Brown Obsessive Compulsive Scale) score.

<sup>f</sup>Effect similar to risperidone in a head-to-head study.

<sup>g</sup>Mean difference of 7.8 points of improvement in the CAPS (Clinician Administered PTSD Scale) score.

<sup>h</sup>Response is defined as at least a 50% improvement in the HAM-A (Hamilton Anxiety Rating Scale) total score.

<sup>i</sup>The evidence for treatment of BPD is inadequate for meta-analysis and does not support conclusions about the statistical or clinical significance of the effect.

**Strength of Evidence Scale**

- High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
- Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.
- Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of effect and is likely to change the estimate.
- Evidence is either unavailable or does not permit a conclusion.

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## Clinical Bottom Line (Continued)

### Other Report Findings About Benefits

#### Dementia

- In general, atypical antipsychotics improve behavioral symptoms of dementia, although effect sizes are small (less than 0.2 standard deviations of difference between treatment and control groups), and important differences are seen in both the benefits and adverse effects across agents. ●●●

#### Obsessive-Compulsive Disorder (OCD)

##### Augmentation of SSRIs

- In head-to-head comparisons:
  - Olanzapine and risperidone are similar in effect for augmentation of SSRIs. ●○○

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### Post-traumatic Stress Disorder (PTSD)

- The evidence is insufficient to determine an effect of risperidone in treating abused women with PTSD.
- The evidence for olanzapine and quetiapine is insufficient for analysis.

### Other Possible Indications

- The evidence for efficacy of atypical antipsychotics as treatment for Tourette's syndrome is insufficient to permit conclusions.

## Adverse Effects

### Elderly Patients\*

- Antipsychotics increase the risk of death in elderly patients with dementia.
  - Of every 100 patients treated with an atypical antipsychotic, 1 died due to treatment with the antipsychotic (NNH = 100) during the 10- to 12-week trials. ●●●
  - The mortality rate during treatment with typical antipsychotics was elevated, when compared with groups not receiving antipsychotics, but the data were not analyzed quantitatively (NNH not available). ●●○
- Risperidone is associated with an increased risk of cerebrovascular accidents (NNH = 34). Both risperidone (NNH = 53) and olanzapine (NNH = 48) are associated with an increased risk of cardiovascular events. ●●○
- In elderly adults, extrapyramidal symptoms (EPSs) are common with risperidone (NNH = 20) and olanzapine (NNH = 10). ●●○
- Atypical antipsychotics are associated with sedative effects (NNH = 8–16) and fatigue (NNH = 18–21). ●●○
- Atypical antipsychotics elevate the risk of urinary adverse effects (infections, incontinence) in elderly patients, but the evidence is too limited to permit conclusions about the degree of risk. ●○○

### Adults Aged 18–64\*

- Antipsychotics in the atypical class in general promote weight gain (also in the elderly) but olanzapine is associated with greater risk than typicals or other atypicals.
  - Olanzapine NNH = 3 versus NNH = 16–35 for other atypicals<sup>†</sup> ●●●
- Some atypical antipsychotics (olanzapine in particular) are associated with endocrine and metabolic abnormalities, but the degree of increased risk is not clear. ●○○
- The risk of EPSs is elevated with aripiprazole (NNH = 11; akathisia NNH = 7), quetiapine (NNH = 36), and ziprasidone (NNH = 24). ●○○
- Atypical antipsychotics (aripiprazole, olanzapine, quetiapine, risperidone, ziprasidone) are associated with sedative effects and fatigue (sedation NNH = 3–11, most pronounced for quetiapine; fatigue NNH = 14–19). ●●○

\* The review of adverse effects is limited to data from studies of off-label use of antipsychotics.

<sup>†</sup> The evidence for ziprasidone is too limited to determine the risk for weight gain.

## Gaps in Knowledge

- The evidence is insufficient to understand the effects of age (with the exception of adverse effects in patients with dementia), race, ethnicity, and baseline severity of disease on outcomes of treatment for off-label indications.
- For most drugs and indications, there are too few studies to permit conclusions about dosage and duration of treatment.
- There are few head-to-head comparisons of atypical and typical antipsychotics, either within or between classes, for treating off-label indications.
- Adverse event reporting is not standardized, preventing global analysis and understanding of risks.
- Evidence about the effects of antipsychotics on endocrine, metabolic, or blood glucose regulation is insufficient to provide clear guidance.

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## What To Discuss With Your Patients

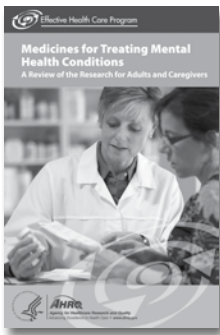
- The potential benefits of antipsychotics for treating disorders that are not psychoses
- The risks of adverse effects, including irreversible extrapyramidal symptoms, when antipsychotics are used
- The trade-offs between benefits and risks for death and stroke for elderly patients with dementia, and considerations of nonpharmaceutical interventions that might be taken before instituting drug treatment
- The likelihood of weight gain with these medicines, and the implications for lifestyle changes that may be necessary
- Patient and caregiver preferences and values regarding treatment

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## Resource for Patients

*Medicines for Treating Mental Health Conditions, A Review of the Research for Adults and Caregivers* is a free companion to this clinician research summary. It covers:

- A description of the antipsychotic medicines in use
- The psychiatric conditions (other than schizophrenia and bipolar disorder) that have been studied for treatment with antipsychotics
- The evidence about the likelihood of short- and long-term benefits from antipsychotic drugs for each condition studied
- The evidence about the risks for adverse effects associated with antipsychotics



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## Ordering Information

For electronic copies of *Medicines for Treating Mental Health Conditions, A Review of the Research for Adults and Caregivers*, this clinician research summary, and the full systematic review, visit [www.effectivehealthcare.ahrq.gov/offlabelantipsych.cfm](http://www.effectivehealthcare.ahrq.gov/offlabelantipsych.cfm). To order free print copies, call the AHRQ Publications Clearinghouse at 800-358-9295.

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## Source

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