

Off-Label Use of ATYPICAL ANTIPSYCHOTIC DRUGS

ATYPICAL ANTIPSYCHOTICS are used primarily for schizophrenia and bipolar mania. They are also prescribed “off label” for symptoms like agitation, anxiety, psychotic episodes, and obsessive behaviors. These drugs can cause serious side effects. Evaluating research about how well atypical antipsychotics work for off-label conditions can help you weigh the benefits and risks of these drugs. The chart on the back page gives information on dosage and price.

ATYPICAL ANTIPSYCHOTICS

Atypical antipsychotics are a newer class of antipsychotic drugs. Compared with the older, “typical,” antipsychotic drugs, such as haloperidol (Haldol®) and chlorpromazine (Thorazine®), atypicals are thought to cause fewer serious or long-term side effects.

The atypical antipsychotic drugs reviewed are:

- Aripiprazole (Abilify®)
- Olanzapine (Zyprexa®)
- Quetiapine (Seroquel®)
- Risperidone (Risperdal®)
- Ziprasidone (Geodon®)

OFF-LABEL USE

“Off label” refers to using a drug for conditions not listed on the Food and Drug Administration (FDA) label of approved uses. Drugs are commonly prescribed off label when approved drugs cannot be used or do not work. Off-label uses may be supported by clinical evidence. This guide covers the off-label use of atypicals for these six conditions:

- Dementia-related behavioral problems
- Depression
- Obsessive-compulsive disorder (OCD)
- Post-traumatic stress disorder (PTSD)
- Personality disorders
- Tourette’s syndrome in children and adolescents

SOURCE

The source material for this summary is a systematic review of over 100 research publications. The review, *Efficacy and Comparative Effectiveness of Off-Label Use of Atypical Antipsychotics* (2007), was prepared by the Southern California/RAND Evidence-based Practice Center. The Agency for Healthcare Research and Quality (AHRQ) funded the systematic review and this guide. The guide was developed using feedback from clinicians and policymakers who reviewed preliminary drafts.

BOTTOM LINE

There is **no strong evidence** that atypical antipsychotics work for any off-label conditions, but there is some **medium level evidence** about their effectiveness for three off-label conditions and about harms.

- **Olanzapine** (Zyprexa®) does not relieve depression for people who have not responded to serotonin reuptake inhibitors (SRIs). This applies to **olanzapine** (Zyprexa®) used alone or in combination with an SRI.

LEVEL OF CONFIDENCE ● ● ○

- Adding **risperidone** (Risperdal®) or **quetiapine** (Seroquel®) to an SRI helps people with obsessive-compulsive disorder who have not responded to standard SRI treatment.

LEVEL OF CONFIDENCE ● ● ○

- **Quetiapine** (Seroquel®), **olanzapine** (Zyprexa®), and **risperidone** (Risperdal®) reduce agitation and behavioral disturbances for people with dementia.

LEVEL OF CONFIDENCE ● ● ○

- **Atypical antipsychotics** increase the risk of death for elderly people with dementia.

LEVEL OF CONFIDENCE ● ● ○

- **Risperidone** (Risperdal®) and **olanzapine** (Zyprexa®) increase the risk of stroke for elderly people with dementia.

LEVEL OF CONFIDENCE ● ● ○

CONFIDENCE SCALE

The confidence ratings are derived from a systematic review of the literature. The level of confidence is based on the overall quantity and quality of clinical evidence.

- ● ● **High** There are consistent results from good quality studies.
- ● ○ **Medium** Findings are supported, but further research could change the conclusions.
- ○ ○ **Low** There are very few studies, or existing studies are flawed.

Using atypicals off label may help people with mental health conditions for which there are no FDA-approved alternatives. The chart on this page lists the results of research on the effectiveness of atypical antipsychotics for off-label conditions. There is insufficient evidence about many of these off-label uses because there are very few research studies, the studies are of poor quality, or study results are inconsistent.

BENEFITS OF ATYPICALS FOR OFF-LABEL CONDITIONS

OFF-LABEL CONDITION ¹	EFFECTIVE (medium level of confidence) ● ● ○	NOT EFFECTIVE (medium level of confidence) ● ● ○	INSUFFICIENT EVIDENCE
Dementia-related behavioral problems	Olanzapine Quetiapine Risperidone		Aripiprazole Ziprasidone
Obsessive-compulsive disorder	Quetiapine ² Risperidone ²		Aripiprazole Olanzapine Ziprasidone
Depression (SRI resistant)		Olanzapine	Aripiprazole Quetiapine Risperidone Ziprasidone
Depression (bipolar)			All atypicals ³
Depression (with psychotic features)			All atypicals
Personality disorders			All atypicals
Post-traumatic stress disorder			All atypicals
Tourette's syndrome in children and adolescents			All atypicals

¹Treatment of adults unless otherwise specified. ²When used in addition to an SRI for people with obsessive-compulsive disorder that does not respond to standard SRI therapy. ³Bipolar depression was an off-label indication at the time of the research studies. In October 2006, the FDA approved quetiapine (Seroquel®) for bipolar depression. SRI = serotonin reuptake inhibitor.

RISKS FOR ELDERLY PEOPLE WITH DEMENTIA

DEATH

All **atypical antipsychotics** increase the risk of death for elderly people with dementia:

- 35 deaths per 1,000 elderly people taking atypicals.
- 23 deaths per 1,000 elderly people taking placebo (inactive substance).
- The risk may be similar when conventional antipsychotics are used for dementia symptoms.

STROKE

Risperidone (Risperdal®) increases the risk of stroke for elderly people with dementia:

- 43 strokes per 1,000 elderly people taking risperidone (Risperdal®).
- 11 strokes per 1,000 elderly people taking placebo.

Olanzapine (Zyprexa®) increases the risk of stroke for elderly people with dementia:

- 13 strokes per 1,000 elderly people taking olanzapine (Zyprexa®).
- 4 strokes per 1,000 elderly people taking placebo.

SIDE EFFECTS FOR CHILDREN AND ADOLESCENTS

There is very little research about the side effects of atypical antipsychotics when used for children and adolescents with Tourette's syndrome. Risperidone (Risperdal®) is the only drug for which we have research about the side effects.

- **Risperidone** (Risperdal®) causes weight gain in children and adolescents. On average, children can gain from 4.5 to 8.5 pounds in 2–3 months of treatment.
- **Risperidone** (Risperdal®) also causes gastrointestinal problems, increased salivation, fatigue, extrapyramidal symptoms (uncontrollable movements), and sleepiness.

SIDE EFFECTS FOR ADULTS: OFF-LABEL CONDITIONS

All of the atypical antipsychotics cause side effects. The chart below shows the side effects for adults taking an atypical antipsychotic for an off-label condition compared with those taking placebo. There are fewer studies of off-label use for some of the atypicals, especially quetiapine (Seroquel®) and ziprasidone (Geodon®). Because most off-label studies lasted less than 6 months, there is limited evidence about longer term side effects.

SIDE EFFECTS	OLANZAPINE (Zyprexa®)	RISPERIDONE (Risperdal®)	ARIPIRAZOLE (Abilify®)	QUETIAPINE (Seroquel®)	ZIPRASIDONE (Geodon®)
Weight gain		INSF	INSF	INSF	INSF
Cardiovascular problems				INSF	INSF
Stroke			INSF	INSF	INSF
Extrapyramidal symptoms (uncontrollable movements)				INSF	
Agitation	INSF	INSF		INSF	INSF
Gait disturbance			INSF	INSF	INSF
Fatigue				INSF	INSF
Sleepiness					
Headache		INSF	INSF	INSF	INSF
Cognitive problems		INSF	INSF	INSF	INSF
Pain	INSF	INSF		INSF	INSF
Gastrointestinal symptoms	INSF				INSF
Urinary symptoms				INSF	INSF
Skin problems	INSF	INSF		INSF	INSF
Dry mouth		INSF	INSF		INSF

The length of the bar indicates how many people typically experience the side effect.

21-50% 11-20% 5-10% Less than 5%

The harmful side effect occurred more often in people taking placebo (inactive substance) than in people taking the drug.

INSF = Insufficient evidence.

SIDE EFFECTS FOR ADULTS: THE CATIE STUDY

There is limited evidence comparing the side effects of atypicals when used off label, but we have comparative data about on-label use for people with schizophrenia. The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) is a large randomized study. It compares side effects of four atypicals—**olanzapine** (Zyprexa®), **quetiapine** (Seroquel®), **risperidone** (Risperdal®), **ziprasidone** (Geodon®)—with perphenazine (Etrafon®, Trilafon®), a conventional (“typical”) antipsychotic. People were followed for up to 18 months.

- Discontinuation due to extrapyramidal symptoms was 2–4 percent with the atypicals compared with 8 percent with the conventional antipsychotic perphenazine (Etrafon®, Trilafon®).
- Sleepiness, dry mouth, and sexual side effects each occurred in 20–30 percent of people with all the study drugs.
- All the study drugs caused weight gain. For some people, the gain was 7 percent or more of their baseline weight (14 lbs or more for someone weighing 200 pounds). The percentage of people gaining 7 percent or more was:
 - 30 percent of people on **olanzapine** (Zyprexa®).
 - 16 percent of people on **quetiapine** (Seroquel®).
 - 14 percent of people on **risperidone** (Risperdal®).
 - 7 percent of people on **ziprasidone** (Geodon®).
 - 12 percent of people on perphenazine (Etrafon®, Trilafon®).
- Discontinuation due to weight gain or metabolic effects was 9 percent in those using **olanzapine** (Zyprexa®) and 1–4 percent in people using the other study drugs.
- Olanzapine** (Zyprexa®) caused greater increases in glycohemoglobin (+ 0.4 percent) and triglycerides (+ 43mg/dl) than the other study drugs.

DOSE AND PRICE OF ATYPICAL ANTIPSYCHOTICS

DRUG NAME ¹	BRAND NAME ²	DAILY DOSE ³		PRICE FOR 1-MONTH SUPPLY ⁴
Aripiprazole	Abilify®	2	mg daily	\$395
		30	mg daily	\$555
Olanzapine	Zyprexa®	2.5	mg daily	\$140
		15	mg daily	\$590
		20	mg daily	\$775
Quetiapine	Seroquel®	50	mg daily	\$105
		200	mg daily	\$210
		600	mg daily	\$550
Risperidone	Risperdal®	0.25	mg twice a day	\$220
		1	mg twice a day	\$255
		2	mg twice a day	\$425
		3	mg twice a day	\$500
Ziprasidone	Geodon®	40	mg twice a day	\$330
		80	mg twice a day	\$375

¹These drugs were evaluated in the systematic review. ²No generics are available.

³Doses are representative of the range used across conditions in the research studies.

⁴Average Wholesale Price from *Drug Topics Redbook*, 2007.

STILL UNKNOWN

- There is no strong evidence on the effectiveness and safety of atypical antipsychotics compared to each other, to conventional (typical) antipsychotics, or to standard treatments for these six off-label conditions.
- Long-term studies have not assessed whether the metabolic changes associated with olanzapine use lead to clinical diabetes.
- We do not know about the long-term effects of off-label use of atypical antipsychotics, because most research studies last 25 weeks or less.

FOR MORE INFORMATION

For electronic copies of this summary and the full systematic review, visit this Web site:

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