Consumer Reports Health.org

BEST BUY DRUGS

Evaluating Prescription Drugs Used to Treat Schizophrenia and Bipolar Disorder:

The Antipsychotics

Comparing Effectiveness, Safety, and Price

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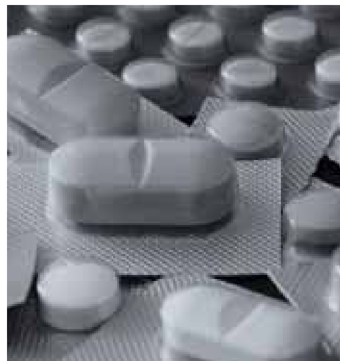

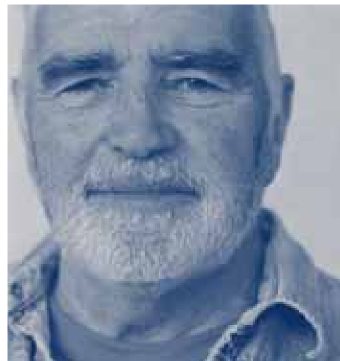

Our Recommendations

Antipsychotic drugs help many people with schizophrenia by suppressing their psychotic symptoms and enabling them to live more meaningful, stable lives with fewer relapses and reducing the need for hospitalization. But this class of medicines has significant limitations. A sizable percentage of people with schizophrenia receive little or no benefit when they take an antipsychotic, and others experience only a partial reduction in symptoms. Also, side effects pose a major barrier to continuous use. In one major study, for example, three of every four people stopped taking an antipsychotic or switched to a different one within 18 months.

Newer and quite expensive antipsychotics marketed heavily to doctors and consumers over the past 15 years have largely eclipsed an older generation of drugs developed in the 1950s and 1960s. Research for years appeared to indicate that the newer drugs were better, largely because they had fewer side effects. But other studies now indicate that overall, the older drugs work just as well at a far lower cost.

Our analysis focused on the use of these drugs in adults. Taking effectiveness, safety, side effects, patient variability, dosing convenience, and cost into account, we have chosen the following as *Consumer Reports Best Buy Drugs:*

- *Generic perphenazine* – for patients with schizophrenia who are not satisfied with their current treatment and whose doctor thinks perphenazine is worth a try. People taking perphenazine should be monitored closely for muscle tremors and spasms.

- *Generic risperidone* – for people with schizophrenia who take perphenazine first and get minimal benefit and/or experience intolerable side effects.

- *Olanzapine (Zyprexa)* – for certain people with schizophrenia who take perphenazine first and receive no benefit (or a minimal one) and/or experience intolerable side effects. Olanzapine is not a good option for people who are overweight or have blood sugar abnormalities, diabetes, or heart disease.

- *Generic clozapine* – for people with moderate to severe schizophrenia who had little to no reduction in symptoms despite trying two or more antipsychotics.

The choice of generic perphenazine—if a person responds well to it—could save you hundreds of dollars a month (adding up to thousands of dollars each year) compared to Zyprexa and Risperdal, the brand-name version of risperidone, depending on the dose required.

We are unable to make a *Best Buy* selection between antipsychotics for people with bipolar disorder. Unfortunately, there is not enough evidence to do so at this time.

This report was updated in August 2009.

Welcome

This report evaluates prescription medicines called antipsychotics. These drugs are used primarily to treat people with schizophrenia. But they are also frequently prescribed to treat people with bipolar disorder (often called manic-depressive disorder). The term "antipsychotic" refers to the fact that the drugs are used, in part, to reduce psychotic symptoms such as hallucinations, delusions, disorganized thinking, and agitation. They are also used to calm disruptive behavior and control aggression.

This report is part of a Consumers Union and *Consumer Reports* project to help you find safe, effective medicines that give you the most value for your health-care dollar. To learn more about the project and other drugs we've evaluated for other diseases and conditions, go online to www.ConsumerReportsHealth.org/BestBuyDrugs.

Schizophrenia

Some three million Americans have schizophrenia. It's an illness that is often mischaracterized in popular culture as having a "split" or "multiple" personalities. But this is entirely inaccurate. People with schizophrenia suffer from disjointed and illogical thinking but they do not have multiple personalities. They may also be withdrawn, fearful and agitated, and experience hallucinations and delusions. And, they may be unable to connect emotionally to others.

Schizophrenia is a chronic disease that, while treatable, is often marked by up and down periods that can put a severe strain on families. Despite that, many affected people live meaningful lives and function well with proper treatment.

The cause of schizophrenia is unknown, but it runs in families and has been clearly linked to biochemical abnormalities in the brain. It affects men and women about equally, and appears to occur at similar rates in all countries and among ethnic groups around the world. Men usually experience the first symptoms in their late teens and early to mid-20s; women are usually first diagnosed a bit later, in their early to mid-20s to mid-30s.

Bipolar Disorder

Bipolar disorder afflicts about five million Americans. The cause is unknown, but it can run in families. The hallmark symptoms are sharp swings between very high moods—called mania—and very low moods—called depression. In most cases these extremes in mood last for several weeks, and there is often an in-between period with a "normal" mood. Some people with bipolar disorder, however, may have periods where symptoms of mania and depression are present simultaneously, in what are called "mixed" episodes.

Men and women are equally likely to have bipolar disorder. It usually strikes people for the first time when they are in their late teens or early 20s, and is then present for life.

About one-third to one-half of people with bipolar disorder have a form of the condition in which they experience more frequent episodes during a year's time – at least four or more – which is referred to as "rapid cycling." The rest are less severely affected and may have months of mood stability between bouts of mania and/or depression. Most people with bipolar disorder are more prone to have shorter periods of mania (from a week or so to several weeks) and longer periods of depression (from several weeks to months).

The symptoms of depression include an overwhelming feeling of sadness, hopelessness, and helplessness, and a loss of pleasure in life. But mania can be just as disturbing. It may be characterized by having boundless energy and feeling especially happy and creative at first. But this high mood often quickly spirals out of control. People with mania can become impatient, irritable, aggressive, and selfish. They may feel constantly agitated, restless, and hyperactive. They may also have racing thoughts, difficulty concentrating, and be easily distracted. And they may be prone to reckless, even destructive, behavior. In a mixed episode, those affected may have all of the boundless energy of mania but also the overwhelming feelings of depression, hopelessness, and helplessness.

When it comes to bipolar disorder, the drugs analyzed in this report are primarily used short-term to treat the manic and mixed phases of the condition, but they are almost never the only drugs used. For example, the drug lithium is often prescribed. Another is the antiseizure medicine valproic acid, also called divalproex sodium (Depakote). People with bipolar disorder may also take antidepressants.

Drugs Covered in This Report

This report focuses primarily on comparing the antipsychotic drugs developed in the past 15 years. These nine newer drugs are often referred to as second-generation, or “atypical,” antipsychotics. This distinguishes them, from a marketing perspective, from a first-generation of antipsychotic drugs developed and widely prescribed beginning in the 1950s. The nine atypical antipsychotic drugs are:

Newer drugs – Atypical Antipsychotics		
Generic Name	**Brand Name(s)**	**Available as a Generic?**
Newer drugs		
1. Aripiprazole	Abilify	No
2. Asenapine*	Saphris	No
3. Clozapine	Clozaril	Yes
4. Iloperidone *	Fanapt	No
5. Olanzapine	Zyprexa, Zyprexa Zydis	No
6. Paliperidone+	Invega	No
7. Quetiapine	Seroquel	No
8. Risperidone+	Risperdal, Risperdal M-Tab	Yes
9. Ziprasidone	Geodon	No

* *Asenapine (Saphris) and illoperidone (Fanapt) were approved by the FDA as this report went to press, so both drugs were not included in the analysis by the Oregon Health & Science University's Drug Effectiveness Review Project, upon which our report is based. However, we discuss both drugs in more detail on page 13.*

+ *Some of these medicines are also available in injectable forms. In particular, risperidone (Risperdal Consta), given every 2 weeks and paliperidone (Invega Sustenna), given once per month. These may be options for people with schizophrenia who refuse or have difficulty remembering to take their medication. However, the injectables are not covered in this report.*

Clozapine (Clozaril) and risperidone (Risperdal) are the only newer drugs currently available as generics.

There are several older antipsychotic drugs still used today, but they have been eclipsed in sales in the last decade by the newer ones because, up until a few years ago, the older ones were thought to be less effective and have worse side effects. But it turns out that side effects remain a serious and troubling issue for both older and newer drugs, and the advantages of the newer drugs over the older ones can no longer be assumed.

The older drug we primarily focus on in this report is perphenazine. That's because it was compared in one major study with the newer drugs and found to be about equal in effectiveness and side effects. Our focus on it—and the data we present on it—does not mean that the other older drugs are not as good. Unfortunately, however, very few long-term studies have compared the older drugs with each other or with the newer drugs.

Examples of Older Drugs*

Generic Name	Brand Name
Chlorpromazine	Thorazine
Haloperidol	Haldol
Loxapine	Loxitane
Molindone	Moban
Perphenazine	Trilafon
Trifluoperazine	Stelazine, Suprazine
Thiothixene	Navane

**Selected older drugs. The list does not include all that are available.*

Off-Label Use

Many of the newer antipsychotic drugs are prescribed "off label" to treat a range of other illnesses and conditions. The term off-label means that the drug is prescribed to treat a condition other than what it was approved for by the Food and Drug Administration (FDA). It is not illegal to prescribe a drug for an off-label purpose, but it is illegal for a drug company to promote such a use.

Antipsychotics are often prescribed off-label to treat people who have had a stroke or suffer from other progressive medical conditions, including dementia-related psychosis (but studies have shown that the drugs increase the risk of death in these patients). They are also sometimes used to treat people with obsessive-compulsive disorder, post-traumatic stress disorder, and personality disorder.

This report does not evaluate the antipsychotics for these off-label uses. We focus only on the use of the drugs for treating people with schizophrenia or bipolar disorder.

The importance of other therapies

Prescription medicines are a mainstay of—and usually the first step in—the treatment of both schizophrenia and bipolar mania disorder. But other treatments are often just as important to meet patients' needs and help them live as normal a life as possible. Chief among these are psychosocial support and rehabilitation through special programs that keep people with schizophrenia from being socially isolated and help them gain employment.

Vocational training and family treatments that focus on providing support, education, and coping skills are also helpful. Such programs don't reduce symptoms or the need for medicines. Indeed, most research has found that a combined approach using psychosocial intervention and optimal drug treatment works best.

This report was released and last updated in August 2009.

What Are the Antipsychotics and Who Needs Them?

The antipsychotics are thought to work by affecting levels of chemicals in the brain called neurotransmitters. In general, almost everyone diagnosed with schizophrenia should be prescribed an antipsychotic at first. For many, these drugs reduce symptoms and improve quality of life, as shown by dozens of studies dating back 40 years.

Indeed, some people with schizophrenia take the drugs for many years, with benefits that allow them to live fulfilling lives outside of mental-health facilities, with fewer (and sometimes no) periods of hospitalization. They pose less harm to themselves and to others as a direct result of the drugs' effects. It is worth noting, too, that before the availability and widespread use of antipsychotics (pre-1960 or so), hundreds of thousands of people with schizophrenia, lacking effective treatment, lived long-term in state mental hospitals.

That said, antipsychotics are far from a panacea in the treatment of this often debilitating disease. They don't significantly help a sizable percentage of people with schizophrenia; others get only a partial reduction in symptoms. And side effects pose a major barrier to continuous use. Studies show that about half of the patients with schizophrenia get a meaningful reduction in symptoms after taking an antipsychotic.

Some symptoms, such as agitation, may get better in just a few days. Others, such as delusions and hallucinations, can take four to six weeks to ease. About 20 percent of people, however, receive virtually no benefit at all from taking an antipsychotic, and 25 percent to 30 percent get a limited benefit. The bar is also set quite low. In studies, a positive response is usually defined as at least a 20 percent improvement/reduction in symptoms. However, the best responders usually have a 50 percent or so reduction in symptoms.

People with schizophrenia may need to be hospitalized or placed into an in-patient mental health clinic, usually when their condition worsens or they have a "psychotic break" or what doctors sometimes call an "exacerbation." As a result, doctors also consider antipsychotic treatment successful if it helps keep people with schizophrenia out of the hospital.

Among people with bipolar disorder, the drugs are mainly measured by their ability to "calm" mania symptoms. All the antipsychotics help in this regard, with 40 percent to 75 percent of the people experiencing a decrease in symptoms. But the drugs have been much less studied in people with bipolar disorder than those with schizophrenia.

Side Effects

Unfortunately, measuring the success of antipsychotics—and comparing them with each other—has become more complicated than simply looking at how they ease symptoms and improve quality of life. That's because both the newer and older antipsychotics cause significant side effects, which limit their overall usefulness. These side effects are listed in Table 1 on page 8.

Simply put, many people who start taking an antipsychotic do not take it for long even if it reduces their symptoms because they cannot or do not wish to tolerate the side effects. In addition, people with schizophrenia and bipolar disorder are highly prone to stopping their medicine because of the nature of their disease; they may deny they need such a strong drug, forget to take it, or quit taking it when symptoms ease. Cost can also be a factor.

While doctors often go to great pains to encourage people with schizophrenia to stay on their "meds," patients often do not do so. This has focused the evaluation of antipsychotics on how many people stay on them and for how long.

Overall, studies indicate that 80 percent to 90 percent of the people who take an antipsychotic will have at least one side effect; most will have more than one. Of those who experience any side effects:

- 20 percent to 30 percent will have a serious or intolerable adverse effect and stop taking the medicine within days, weeks, or a few months.
- 35 percent to 45 percent will stop taking the medicine within six months.
- 65 percent to 80 percent will stop taking the medicine within 12 to 18 months. Many who stop one

antipsychotic will try another, but a pattern of stopping and starting with another drug is common and not always productive.

These results from studies raise the question of how best to use antipsychotics. These days, doctors will weigh a variety of factors to help them decide if an antipsychotic should be prescribed, and if so, which one and at what dosage.

While fully recognizing that treatment of schizophrenia must be tailored to each patient, we offer the following general guidance:

- Repeating our advice above, all people newly diagnosed with schizophrenia should try an antipsychotic. They may respond well with minimal side effects. They should try to persevere for a few months through what can be a frustrating period when the drug does not seem to be helping

Table 1. Antipsychotic Side Effects

Minor to severe side effects

These can ease or disappear over time, or be reduced if dose is lowered. They disappear when the drug is stopped. The list below is alphabetical and not in any order of importance or severity. Most people have more than one of these effects. But experience with, and severity of, side effects varies substantially.

- Abnormal limb and body movements, muscle twitches, tremors and spasms
- Abnormal menstruation
- Blurred vision
- Constipation
- Dizziness on standing or moving quickly
- Dry mouth
- Excessive salivation
- Feeling more hungry than usual
- Insomnia
- Lack of coordination
- Lip smacking and abnormal tongue movements
- Male infertility
- Muscle stiffness
- Muscle weakness
- Rapid heartbeat
- Restlessness
- Sedation, drowsiness
- Sensitivity to sunlight
- Sexual dysfunction
- Skin rashes
- Slurred speech

May be serious

These may require discontinuing the drug; can in some cases become permanent.

- **Agranulocytosis**—the failure of the bone marrow to produce disease-fighting white blood cells, which can lead to serious or fatal infections. (This risk is associated primarily with clozapine [regular blood tests are required with use], but it has also been reported with other antipsychotics.)
- **Changes in metabolism** that cause blood sugar abnormalities and other problems, which can lead to diabetes and a higher risk of heart disease and strokes.
- **Myocarditis**—an inflammation of the heart muscle that can be fatal. (This risk associated primarily with clozapine.)
- **Neuroleptic Malignant Syndrome**—characterized by high fever, increased heart rate, and blood pressure; can be fatal.
- **Seizures.**
- **Significant weight gain**—7 percent or greater increase in pretreatment body weight. (Generally this is about 12 pounds or more.)
- **Tardive dyskinesia**—characterized by uncontrollable body movement that may include tremors and spasms.

much, but may cause some initial (but perhaps not serious or long-lasting) side effects.

- Failure to respond to an initial antipsychotic drug should lead to trying another one.
- Don't take more than one antipsychotic medicine at the same time. This increases the risks of side effects, and the benefits are unproven.
- People with severe or acute symptoms—or who have frequent psychotic breaks —should take an antipsychotic even if the side effects are difficult to tolerate. Family and caregivers should make extra efforts to ensure that they stay on the drugs.
- People who have only mild symptoms or who are responding well to nondrug treatment should consider switching to another drug that may be better tolerated, or—only if necessary—discontinuing their antipsychotic medicine if the side effects are outweighing the benefits.
- People who are achieving good control of their condition with an older drug, with tolerable side effects, should not switch to a newer drug.
- People at risk for diabetes and heart disease, and those who are obese should take special care in choosing an antipsychotic drug since several of the drugs increase the risk of those conditions more than others.

Cost Issues with Antipsychotics

The treatment of schizophrenia with antipsychotics is also complicated by cost issues. Most of the older drugs are relatively inexpensive, but the newer ones are quite costly. Recent years have seen a shift to these newer, more expensive drugs. The problem is that a vast majority of people with schizophrenia are unemployed or are minimally employed. Many also lack health insurance. And of those who do have health insurance, over half are covered under public programs such as Medicaid and Medicare as disabled people.

Both those programs provide fairly open access to the newer drugs. As a result, the newer drugs cost the programs an estimated $5 billion to $7 billon a year. Doctors are being urged to prescribe the newer antipsychotics judiciously, and only for schizophrenia patients who really need them and for whom the benefits clearly outweigh the risks. We concur with that advice, and recommend starting with a less expensive older drug. (More about this in the next section.)

However, cost should never be the most important determinant of treatment. If a patient does not respond to an older antipsychotic, his or her access to a more expensive newer drug should not be restricted. Likewise, a patient who is well-controlled, with tolerable side effects, on a newer medicine should not be asked to switch to an older one just because it is less expensive.

For people with bipolar disorder, antipsychotics are not the only drug treatment option, nor are they a good first choice. Lithium continues to be the standard treatment. The drugs carbamazepine (Equetro) and valproic acid—which is also called divalproex sodium (Depakote)—are also now widely used, and are proven effective. All are available as low-cost generic drugs.

Antipsychotics are often used as an add-on to other medications in the treatment of people with bipolar disorder. For example, an antipsychotic is often prescribed with lithium or valproic acid for people in the midst of a severe manic episode. After the symptoms are stabilized, doctors usually reassess the need for ongoing antipsychotic treatment and discontinue the antipsychotic medication unless it is required to control persistent psychotic behavior and symptoms. Recent study results discussed in this report should give further pause to the regular use of antipsychotics to treat bipolar mania.

Choosing an Antipsychotic – Our *Best Buy* Picks

The newer antipsychotics have been compared with each other and with some of the older drugs in large-scale studies that have helped clarify the strengths and weaknesses of each medicine. However, studies can never reveal whether or how much any person will benefit from a particular drug or the side effects they will experience. And as mentioned above, it's quite often the case with mental-health drugs that a patient will have to try two or even three medicines before finding one that works.

There are four important things you need to know as you and your doctor consider the options.

(1) The newer antipsychotic drugs are no more effective than the older ones. Studies have proven wrong the assumption that the newer drugs work better, with the exception of clozapine for treatment-resistant patients.

(2) In terms of overall effectiveness, clozapine (Clozaril), olanzapine (Zyprexa), quetiapine (Seroquel), and risperidone (Risperdal) have the strongest evidence among the newer antipsychotic drugs. But the main differences among the newer antipsychotic drugs–often substantial–mainly come from the side effects and problems they can cause.

(3) The available evidence indicates that the newer drugs are no safer or less likely to cause side effects (including serious ones) than the older drugs. However, some newer drugs appear to cause fewer muscle and body movement problems in some patients.

(4) The newer drugs cost many times more than perphenazine. (See Table 3 on pages 14-16.)

For the short-term, the newer antipsychotic drugs have been proven to help relieve the symptoms of schizophrenia in 45 percent to 80 percent of people who take them. To give you a better understanding of how the antipsychotics compare with each other on the longer-term, Table 2 on page 11 shows a number of the more important measures of patient response and side effects for the newer medicines and an older drug, perphenazine. The data from Table 2 come from a landmark study called the Clinical Antipsychotic Trials of Intervention Effectiveness, or CATIE for short. CATIE is the most comprehensive study comparing the antipsychotics. The data in Table 2 apply to treatment of people with schizophrenia, not bipolar disorder.

Starting below, we discuss each drug, in turn, based on information from recent studies.

Ziprasidone (Geodon). Geodon had a fairly high rate of treatment drop-out at 18 months (80 percent) and hospitalization for worsening schizophrenia. On the other hand, Geodon apparently presents a substantially lower risk of weight gain than other antipsychotics. However, Geodon has been associated with a risk of abnormalities in the electrical signals of the heart, which can lead to heart-rhythm disturbances, fainting, and even death. So far no formal studies link Geodon to higher rates of these serious outcomes compared with other antipsychotics. Still, we consider Geodon a poor first choice among newer antipsychotics at this point, except perhaps for people who are significantly overweight.

Quetiapine (Seroquel). This drug had the highest rate of discontinuation and hospitalization for recurrence of symptoms. Along with Geodon, we consider Seroquel a poor first choice among the newer antipsychotics. It has no apparent advantages over the other drugs.

Olanzapine (Zyprexa). This drug presents a mixed picture. It had the lowest rate of treatment failure, treatment dropout, relapse, and hospitalization for worsening of condition. It also has the longest "treatment duration," the length of time patients stay on the drug before quitting. Olanzapine is also one of the few newer antipsychotic drugs that have recently been proven to improve overall quality of life in a large-scale study. On the other hand, it had the highest rate by far of significant weight gain and the highest rate (albeit just slightly) of intolerable side effects. People taking Zyprexa gained an average of two pounds a month. Studies show it is also more likely to cause metabolic side effects, such as elevated cholesterol and blood sugar.

Zyprexa is a not a good choice for people who are already overweight or have heart disease or diabetes.

Table 2. Comparing Antipsychotic Drugs to Treat Schizophrenia[1]							
Branded-drug (Generic name)	Discontinuation Rate Over 18 Months – Stopped Taking the Medicine	Hospitalized for Worsening Schizophrenia	Treatment Didn't Work	Intolerable Side Effects[2]	Significant Weight Gain[3]	Prolactin Elevation[4]	Serious Side Effect[5]
Olanzapine (Zyprexa)	68%	11%	15%	18%	30%	No	10%
Quetiapine (Seroquel)	82	20	28	15	16	No	9
Risperidone (Risperdal)	76	15	27	10	14	Yes	10
Ziprasidone (Geodon)	80	18	24	15	7	No	10
Perphenazine[6] (Generic)	75	16	25	16	12	No	11

1. The results presented in this table are based on a landmark study called the Clinical Antipsychotic Trials of Intervention Effectiveness, or CATIE for short. CATIE is the most comprehensive study comparing the antipsychotics. It was funded and overseen by the National Institute of Mental Health, part of the National Institutes of Health. The results were published in the New England Journal of Medicine on Sept. 22, 2005; Vol. 353, No. 12; pages 1209-1223. The 1,493 patients in the study were followed for 18 months.
2. Usually led to stopping the drug right away.
3. Reflects only those who gained 7 percent or more of their starting body weight (that's about 12 pounds for a 175 pound person). That is considered a cut-off of significant weight gain. Others in the trial gained weight but not up to the 7 percent level.
4. Elevations in prolactin can lead to sexual and reproductive difficulties and abnormalities in breast glands for both women and men. It can also cause irregular menstruation in women.
5. These were side effects that usually required reducing the dose or stopping the medicine, or treatment for the side effect.
6. Perphenazine is a first-generation antipsychotic, available as a generic.

It may also present a greater risk of side effects in people who are prone to these conditions. But for many people with schizophenia, it is a viable starting point.

It may also be a good choice for people who have failed to respond to one antipsychotic already. In a key study that looked at how patients who failed on one drug fared on a second, more patients were able to continue taking Zyprexa compared with Geodon and Seroquel.

Risperidone (Risperdal). This drug had the lowest rate of intolerable side effects, which usually lead to stopping the medicine right away. Also, like Zyprexa, Risperdal was found to improve overall quality of life in a large-scale study. But long-term dropout for Risperdal was about the same as with other drugs. It also had somewhat more discontinuations due to lack of effectiveness. Risperdal is available as a generic, but the cost is not all that much lower than that of some of the other newer brand-name antipsychotic drugs, and it is still much more expensive than generic perphenazine. We consider risperidone a good choice for most people with schizophrenia who have already tried perphenazine and did not have a good response or who were unable to tolerate the side effects.

In the same study cited above under the Zyprexa section, fewer such patients discontinued Risperdal than Geodon, Seroquel, or Zyprexa.

Clozapine (Clozaril, Fazacio). This drug, which first became available in 1989, was the first of the newer antipsychotics. It is available as both a brand-name and a generic. It performs well against the other drugs but is not a good first-choice option. That's

because of the well-established risk it poses of seizures and a life-threatening side effect called agranulocytosis (bone-marrow failure), which can lead to serious or fatal infections. Approximately 4 percent of the patients taking clozapine have seizures. About 1 percent will develop agranulocytosis. Agranulocytosis can be detected through regular blood tests. Clozapine also appears to cause more sedation than the other drugs.

Because of the risk it poses, clozapine is prescribed only for people with schizophrenia who have not benefited from any other antipsychotic drug. These patients are often referred to as "treatment resistant." Several studies have found clozapine more effective at reducing symptoms and preventing hospitalization than any other antipsychotic for people who have failed on the other drugs. In one study, for example, 44 percent of the people who switched to clozapine stayed on it for 18 months compared with just 18 percent who switched to another newer antipsychotic. And on average, patients stayed on clozapine for 10 months compared with just three months for the other drugs. Also, clozapine may be a good option for people with schizophrenia who have a history of suicide attempts as it was found superior to olanzapine (Zyprexa) in preventing suicides and decreasing suicidal thinking over two years in a good-quality trial of people considered at high risk of suicide.

Aripiprazole (Abilify). This drug was not included in the large-scale studies and has been less studied than the other drugs. Some evidence suggests that Abilify may pose less risk of weight gain and blood sugar problems, but studies have not yet proved that conclusively. Abilify has been heavily advertised to doctors and consumers recently for the treatment of bipolar mania and as an add-on drug for depression. As stated earlier, the regular or routine prescribing of any of the newer antipsychotics to treat people with bipolar mania should be re-evaluated and perhaps done more cautiously than in the past. The available evidence for Abilify does not allow us to make a clear recommendation for its use in people with schizophrenia.

Paliperidone (Invega). This drug was approved in December 2006 primarily based on evidence from two six-week trials in which it was found to be superior to placebo in short-term response rates and to have a lower treatment dropout rate. So far there is no indication that Invega poses a higher risk of weight gain, elevated blood sugar, or cholesterol, at least in the short-term, than some of the other newer antipsychotics. But there is some evidence that it may cause some potentially dangerous changes in some patients' heart rhythms. For this reason, it might be a good idea for people with a history of heart problems to avoid it. Overall, because the safety profile of Invega is not as well established as some of the other drugs, we do not recommend it as a good first or second choice for the treatment of schizophrenia.

Iloperidone (Fanapt). This drug was recently approved (May 2009). Preliminary evidence shows that Fanapt may increase your risk of experiencing some potentially dangerous changes in your heart rhythms. Therefore, Fanapt should be avoided by people with a history of heart problems. Because Fanapt is so new, its safety profile is not as well established as some of the other drugs, so we do not recommend it as a first or second choice for treatment of schizophrenia.

Asenapine (Saphris). This drug was approved by the FDA for treating schizophrenia and bipolar disorder as our report went to press (August 2009). It was not included in our analysis or in the analysis done by DERP, which our report is based on. We recommend avoiding Saphris for the time-being. There are few available studies involving the drug and its safety profile is not fully established yet, so at this point, it is too early to draw conclusions about how Saphris might stack up against the other antipsychotics. In addition, since it is a new drug, its likely to be very expensive compared to some of the other, less costly antipsychotics, such as perphenazine.

Generic perphenazine. This is an older antipsychotic that has been prescribed to treat schizophrenia since the 1970s. A major study found that it ranked roughly equally with the newer drugs in terms of effectiveness, treatment dropout, and most side effects. However, it does carry a higher risk of more movement problems and tardive dyskinesia.

Other older drugs. An important study conducted in England that was published in October 2006 compared what happened to people with schizophrenia taking one of several older antipsychotics with those

taking one of the newer drugs. All the people in the study were switched from a drug that had not helped them to another drug. After a year, the patients taking both older and newer drugs fared about the same in terms of reduction of symptoms, side effects, and overall quality of life.

However, this study did not compare individual drugs, but instead compared the older drugs as a group with the newer drugs as a group. So it does not allow us to draw conclusions about the safety or effectiveness of specific drugs.

Bipolar disorder. As previously stated, the atypical antipsychotics have been less studied in treating bipolar disorder compared with schizophrenia. Only two small head-to-head trials have been done, but neither showed one drug to be clearly superior to the others. As a result, we are unable to make a *Best Buy* selection between antipsychotics for people with bipolar disorder. Unfortunately, there is not enough evidence to do so.

Taking effectiveness, safety, side effects, dosing convenience, patient variability, and cost into account, we have chosen the following as *Consumer Reports Best Buy Drugs* to treat schizophrenia:

- *Generic perphenazine* – for patients with schizophrenia who are not satisfied with their current treatment and whose doctor thinks perphenazine is worth a try. Patients taking perphenazine should be monitored closely for muscle tremors and spasms.
- *Generic risperidone* – for people with schizophrenia who take perphenazine first and get minimal benefit and/or experience intolerable side effects.
- *Olanzapine (Zyprexa)* – for certain people with schizophrenia who take perphenazine first and receive no benefit (or a minimal one) and/or experience intolerable side effects. Olanzapine is not a good option for people who are overweight or have blood sugar abnormalities, diabetes, or heart disease.
- *Generic clozapine* – for people with moderate to severe schizophrenia who have not responded at all to two or more antipsychotics and have had little reduction in symptoms.

Our recommendations include all doses. The dose at which antipsychotics are prescribed is a decision to be made by doctors based on a variety of factors for each individual patient. As with all drugs, the dose balances the need to achieve optimal effectiveness with the need to limit side effects. With antipsychotics, this balance can be especially challenging to achieve.

In addition, because of their chemical nature and the broad spectrum of patient response, the antipsychotics are prescribed in a wide range of doses. Doctors usually begin people on low doses to gauge their response and experience of side effects. The dose is then usually increased. (In general, higher doses of older drugs like perphenazine should be avoided because they are associated with a higher risk of side effects.)

Dose affects cost, too. Higher doses of most antipsychotics cost more, sometimes significantly more, as you can see in Table 3. Also, one of the *Best Buy* selections, generic risperidone, is also available as a dissolvable tablet. It is more expensive, but may be worth it if a person is unable to swallow a standard tablet.

Perphenazine is by far the least expensive of our *Best Buy* choices, costing $75 to $117 per month depending on the dose needed. We choose perphenazine as a *Best Buy* because a major U.S. study found it was roughly equivalent in effectiveness and side effects to the newer, more expensive drugs. We should note, however, that in light of recent studies, doctors may now be more willing to try other older antipsychotics. Many of them are inexpensive generics that cost even less than perphenazine.

Our choice of Zyprexa and generic risperidone was driven by the evidence presented starting on page 10. They are expensive newer drugs. But overall, they are the two best choices if perphenazine or another drug does not work. Note also that both these drugs offer the convenience of once-a-day dosing at some dose strengths.

Generic clozapine is the best option for people who have failed with at least two drugs, because studies show that it can help in these cases. For

the patients who fall into this category, clozapine may be a last best shot at symptom reduction. At most doses, generic clozapine is substantially less expensive than Zyprexa or generic risperidone.

The savings available from choosing generic perphenazine first is significant. If a patient responds well to this drug, he or she could save hundreds of dollars a month (amounting to thousands of dollars per year) compared with Zyprexa and generic risperidone depending on the dose required. As can also be gleaned from Table 3, other older antipsychotics may yield even greater savings compared with the expensive newer drugs.

Table 3. The Antipsychotic Drugs – Cost Comparison

*The older drugs are in italics. The newer ones are in regular text.**

Generic Name and Strength	Brand Name	Number of tablets or capsules per day[1]	Total Daily Dose	Average Monthly Cost[2]
Aripiprazole target daily dose = 10 mg -15 mg				
Aripiprazole 10 mg tablet	Abilify	One	10 mg	$589
Aripiprazole 15 mg tablet	Abilify	One	15 mg	$576
Aripiprazole 10 mg dissolvable tablet	Abilify	One	10 mg	$707
Aripiprazole 15 mg dissolvable tablet	Abilify	One	15 mg	$597
Asenapine	Saphris	Not available	Not available	Not available
Chlorpromazine target daily dose = 200 mg				
Chlorpromazine 100 mg tablet	Generic	Two	200 mg	$38
Chlorpromazine 200 mg tablet	Generic	One	200 mg	$23
Clozapine target daily dose = 300 mg - 450 mg				
CR BEST BUY Clozapine 100 mg tablet	Generic	Three	300 mg	$278
Clozapine 100 mg tablet	Clozaril	Three	300 mg	$690
CR BEST BUY Clozapine 200 mg tablet	Generic	Two	400 mg	$398
Clozapine 100 mg dissolvable tablet	Fazacio ODT	Three	300 mg	$618
Haloperidol target daily dose = 0.5 mg - 5 mg two or three times daily				
Haloperidol 0.5 mg tablet	Generic	Two-Three	1 mg - 1.5 mg	$14-$21
Haloperidol 1 mg tablet	Generic	Two-Three	2 mg - 3 mg	$14-$21
Haloperidol 2 mg tablet	Generic	Two-Three	4 mg - 6 mg	$16-$24
Haloperidol 5 mg tablet	Generic	Two-Three	10 mg - 15 mg	$18-$27
Iloperidone target daily dose = 12 mg - 24 mg				
Iloperidone 6 mg tablet	Fanapt	Two	12 mg	Price not available
Iloperidone 8 mg tablet	Fanapt	Two	16 mg	Price not available
Iloperidone 10 mg tablet	Fanapt	Two	20 mg	Price not available
Iloperidone 12 mg tablet	Fanapt	Two	24 mg	Price not available
Loxapine target daily dose = 20 mg - 60 mg				
Loxapine 10 mg capsule	Generic	Two-Three	20 mg - 30 mg	$68-$102
Loxapine 25 mg capsule	Generic	One-Two	25 mg - 50 mg	$48-$96
Loxapine 50 mg capsule	Generic	One	50 mg	$68

Table 3. The Antipsychotic Drugs – Cost Comparison

*The older drugs are in italics. The newer ones are in regular text.**

	Generic Name and Strength	Brand Name	Number of tablets or capsules per day[1]	Total Daily Dose	Average Monthly Cost[2]
	Molindone target daily dose = 100 mg				
	Molindone 25 mg tablet	Moban	Four	100 mg	$552
	Molindone 50 mg tablet	Moban	Two	100 mg	$260
	Olanzapine target daily dose = 10 mg				
CR BEST BUY	Olanzapine 10 mg tablet	Zyprexa	One	10 mg	$546
	Olanzapine 10 mg dissolvable tablet	Zyprexa Zydis	One	10 mg	$641
	Paliperidone target daily dose = 6 mg				
	Paliperidone 6 mg sustained release tablet	Invega	One	6 mg	$532
	Perphenazine target daily dose = 4 mg - 8 mg three times daily				
CR BEST BUY	*Perphenazine 2 mg tablet*	Generic	Three	6 mg	$75
CR BEST BUY	*Perphenazine 4 mg tablet*	Generic	Three	12 mg	$102
CR BEST BUY	*Perphenazine 8 mg tablet*	Generic	Three	24 mg	$117
	Quetiapine target daily dose range = 300 mg - 400 mg				
	Quetiapine 100 mg tablet	Seroquel	Three	300 mg	$549
	Quetiapine 200 mg tablet	Seroquel	Two	400 mg	$688
	Quetiapine 300 mg tablet	Seroquel	One	300 mg	$442
	Quetiapine 400 mg tablet	Seroquel	One	400 mg	$517
	Quetiapine sustained release target daily dose = 400 mg - 800 mg				
	Quetiapine 400 mg sustained release tablet	Seroquel XR	One-Two	400 mg	$511-$1022
	Risperidone target daily dose = 2 mg - 8 mg				
CR BEST BUY	Risperidone 1 mg tablet	Generic	Two	2 mg	$256
	Risperidone 1 mg dissolvable tablet	Generic	Two	2 mg	$406
	Risperidone 1 mg tablet	Risperdal	Two	2 mg	$450
	Risperidone 1 mg dissolvable tablet	Risperdal	Two	2 mg	$616
CR BEST BUY	Risperidone 2 mg tablet	Generic	One-Two	2 mg - 4 mg	$206-$412
	Risperidone 2 mg dissolvable tablet	Generic	One-Two	2 mg - 4 mg	$296-$592
	Risperidone 2 mg tablet	Risperdal	One-Two	2 mg - 4 mg	$382-$764
	Risperidone 2 mg dissolvable tablet	Risperdal	One-Two	2 mg - 4 mg	$431-$862
CR BEST BUY	Risperidone 3 mg tablet	Generic	One-Two	3 mg - 6 mg	$238-$476
	Risperidone 3 mg dissolvable tablet	Generic	One-Two	3 mg - 6 mg	$369-$738
	Risperidone 3 mg tablet	Risperdal	One-Two	3 mg - 6 mg	$425-$850
	Risperidone 3 mg dissolvable tablet	Risperdal	One-Two	3 mg - 6 mg	$548-$1,096
CR BEST BUY	Risperidone 4 mg tablet	Generic	One-Two	4 mg - 8 mg	$327-$654

Table 3. The Antipsychotic Drugs – Cost Comparison *The older drugs are in italics. The newer ones are in regular text.**				
Generic Name and Strength	Brand Name	Number of tablets or capsules per day[1]	Total Daily Dose	Average Monthly Cost[2]
Risperidone 4 mg dissolvable tablet	Generic	One-Two	4 mg - 8 mg	$479-$958
Risperidone 4 mg tablet	Risperdal	One-Two	4 mg - 8 mg	$601-$1,202
Risperidone 4 mg dissolvable tablet	Risperdal	One-Two	4 mg - 8 mg	$717-$1,434
Thiothixene target daily dose = 20 mg - 30 mg				
Thiothixene 10 mg capsule	Generic	Two-Three	20 mg - 30 mg	$34-$51
Trifluoperazine target daily dose = 15 mg - 20 mg				
Trifluoperazine 5 mg	Generic	Three	15 mg	$66
Trifluoperazine 10 mg	Generic	Two	20 mg	$62
Ziprasidone target daily dose = 20 mg - 80 mg twice daily				
Ziprasidone 20 mg capsule	Geodon	Two	40 mg	$538
Ziprasidone 40 mg capsule	Geodon	Two	80 mg	$518
Ziprasidone 60 mg capsule	Geodon	Two	120 mg	$628
Ziprasidone 80 mg capsule	Geodon	Two	160 mg	$622

* For the first-generation drugs – names are listed in italics – only the monthly costs of the generics are given, except for molindone (Moban); no generic of Moban is yet available.

1. As typically prescribed for schizophrenia. The dose ranges come from the FDA approved labels (package inserts) for these drugs. All the antipsychotics are prescribed in a wide range of doses to meet patients' individual needs. Most people are started on low doses to gauge their response and experience of side effects. The dose is then usually increased, sometimes substantially. We have used the"target dose" suggestion – the dose that the drugs' labels have stated as being effective for most patients.
2. Prices reflect nationwide retail average for May 2009, rounded to the nearest dollar. Information derived by *Consumer Reports Best Buy Drugs* from data provided by Wolters Kluwer Health, Pharmaceutical Audit Suite®. Wolters Kluwer Health is not involved in our analysis or recommendations.

Table 4. Typical Starting Dose of Antipsychotics

Note: The starting doses listed here are taken from the drugs' FDA approved labels (package inserts). But you should know that finding the right dose for each person is highly variable with these medicines, so a doctor may decide to start with a higher or lower dose, depending on a patient's unique situation and the status of their condition. If the drug is tolerated at the starting dose, then the next step is to find the right level that controls symptoms. That may be a lower or higher dose that, again, will vary from person to person.

Generic Name*	Brand Name	Starting Daily Dose
Aripiprazole	Abilify	10 mg - 15 mg
Asenapine	Saphris	Not available
Chlorpromazine	Generic	10 mg three or four times daily; or 25 mg two or three times daily
Clozapine	Clozaril, Fazacio ODT	12.5 mg once or twice daily
Haloperidol	Generic	0.5 mg – 2 mg two or three times daily
Iloperidone	Fanapt	1 mg twice daily
Loxapine	Generic	10 mg twice daily
Molindone	Moban	50 mg - 75 mg
Olanzapine	Zyprexa, Zyprexa Zydis	5 mg - 10 mg
Paliperidone	Invega	6 mg
Perphenazine	Generic	4 mg - 8 mg three times daily
Quetiapine	Seroquel	25 mg twice daily
Quetiapine sustained release	Seroquel XR	300 mg
Risperidone	Risperdal	1 mg
Thiothixene	Generic	2 mg - 5 mg three times daily
Trifluoperazine	Generic	2 mg - 5 mg twice daily
Ziprasidone	Geodon	20 mg twice daily

* The older drugs are in italics. The newer ones are in regular text.

Talking With Your Doctor

It's important for you to know that the information we present here is not meant to substitute for a doctor's judgment. But we hope it will help you and your doctor arrive at a decision about which antipsychotic medication and dose is best for you, and which gives you the most value for your health-care dollar.

Bear in mind that many people are reluctant to discuss the cost of medicines with their doctor and that studies show doctors do not routinely take price into account when prescribing medicines. Unless you bring it up, your doctors may assume that cost is *not* a factor for you.

Many people (including physicians) think that newer drugs are better. While that's a natural assumption to make, it's not usually true. Studies consistently show that many older medicines are as good as, and in some cases better than, newer medicines. Think of them as "tried and true," particularly when it comes to their safety record. Newer drugs have not yet met the test of time, and unexpected problems can and do crop up once they become available on the market.

Of course, some newer prescription drugs are indeed more effective and safer. Talk with your doctor about the pluses and minuses of newer versus older medicines, including generic drugs.

Prescription medicines go "generic" when a company's patents on a drug lapse, usually after about 12 to 15 years. At that point, other companies can make and sell the drug.

Generics are much less expensive than newer brand-name medicines but they are *not* lesser quality drugs. Indeed, most generics remain useful medicines even many years after first being marketed. That is why today more than 60% of all prescriptions in the U.S. are written for generics.

Another important issue to talk with your doctor about is keeping a record of the drugs you are taking. There are several reasons for this:

- First, if you see several doctors, each may not be aware of medicines the others have prescribed.
- Second, since people differ in their response to medications, it is very common for doctors today to prescribe several medicines before finding one that works well or best.
- Third, many people take several prescription medications, nonprescription drugs and dietary supplements at the same time. These can interact in ways that can either reduce the benefit you get from the drug or be dangerous.
- And fourth, the names of prescription drugs—both generic and brand—are often hard to pronounce and remember.

For all these reasons, it's important to keep a *written list* of all the drugs and supplements you are taking, and to periodically review this list with your doctors.

Always be sure, too, that you understand the dose of the medicine being prescribed for you and how many pills you are expected to take each day. Your doctor should tell you this information. When you fill a prescription at a pharmacy, or if you get it by mail, you may want to check to see that the dose and the number of pills per day on the pill bottle match the amounts that your doctor told you.

How We Picked the *Best Buy* Drugs

Our evaluation is based in part on an independent scientific review of the studies and research literature on the newer antipsychotic drugs conducted by a team of physicians and researchers at the Oregon Health & Science University Evidence-based Practice Center. This analysis, which reviewed hundreds of studies including those conducted by the drugs' manufacturers, was conducted as part of the Drug Effectiveness Review Project, or DERP. DERP is a first-of-its-kind, an 11-state initiative to evaluate the comparative effectiveness and safety of hundreds of prescription drugs.

A synopsis of DERP's analysis of the antipsychotic drugs forms the basis for this report. A consultant to *Consumer Reports Best Buy Drugs* is also a member of the Oregon-based research team, which has no financial interest in any pharmaceutical company or product.

The full DERP review of the antipsychotic drugs is available at http://www.ohsu.edu/ohsuedu/research/policycenter/DERP/about/final-products.cfm. (This is a long and technical document written for physicians.)

Our analysis also relied on the results of several major studies. Most notably, it relied on the results of the Clinical Antipsychotic Trials of Intervention Effectiveness, or CATIE for short. CATIE is the most comprehensive study to date that directly compares the effectiveness of antipsychotic drugs. The study was funded and overseen by the National Institute of Mental Health, part of the National Institutes of Health. The main results were published in the *New England Journal of Medicine* on Sept. 22, 2005 (Lieberman et al., "Effectiveness of Antipsychotic Drugs in Patients with Chronic Schizophrenia," Vol. 353, No. 12; pages 1209-1223).

We also drew on the results of a study published in October 2006 in the *Archives of General Psychiatry* (Jones PB et al., Vol. 63, pages 1079-1087), and commentary that accompanied the publication of this study. The study was titled "Randomized Controlled Trial of the Effect on Quality of Life of Second vs. First-Generation Antipsychotic Drugs in Schizophrenia."

Finally, we were aided by analysis and data presented in two other resources: (1) "Guidance on the Use of Newer (Atypical) Antipsychotic Drugs for the Treatment of Schizophrenia," a report by the National Institute for Clinical Excellence in England; and (2) "Drugs for Psychiatric Disorders," Treatment Guidelines from *The Medical Letter* (June 2006, Vol. 4, No. 46).

The monthly costs we cite were obtained from a health-care information company that tracks the retail sales of prescription drugs in the U.S. Prices for a drug can vary quite widely. All the prices in this report are national averages based on sales in retail outlets. They reflect the cash price paid for a month's supply of each drug in May 2009.

Consumers Union and *Consumer Reports* selected the *Best Buy Drugs* using the following criteria. The drug had to:

- Be approved by the FDA to treat schizophrenia.
- Be as effective as or more effective than other schizophrenia medicines when prescribed appropriately according to FDA guidelines.
- Have a safety record equal to or better than other schizophrenia medicines when prescribed appropriately. The *Consumers Reports Best Buy Drugs* methodology is described in more detail in the Methods section at www.ConsumerReportsHealth.org/BestBuyDrugs.

About Us

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Consumer Reports Best Buy Drugs is a public-education project administered by Consumers Union. Two outside sources of generous funding made the project possible. They are a major grant from the Engelberg Foundation, a private philanthropy, and a supporting grant from the National Library of Medicine, part of the National Institutes of Health. A more detailed explanation of the project is available at www.ConsumerReportsHealth.org/BestBuyDrugs.

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References

The first reference on this list is to the Drug Effectiveness Review Project Report on antipsychotic drugs. That report was the main resource for our evaluation. We refer you to it for a comprehensive list of studies and medical literature citations. The other references we list here are the principal sources of information used to produce this Consumer Reports Best Buy Drugs analysis of antipsychotic medicines.

1. McDonagh M.S., et al., *Drug Class Review on Atypical Antipsychotic Drugs*. The Drug Effectiveness Review Project. Final Report Update 2, June, 2008. http://www.ohsu.edu/ohsuedu/research/policycenter/DERP/about/final-products.cfm.
2. Lieberman J.A., et al., "Effectiveness of antipsychotic drugs in patients with chronic schizophrenia." *New England Journal of Medicine* (Sept. 22, 2005); 353(12):1209-1223.
3. Jones P.B., et al., "Randomized Controlled Trial of the Effect on Quality of Life of Second- vs. First-Generation Antipsychotic Drugs in Schizophrenia: Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (Cutlass1)," *Archives of General Psychiatry* (October 2006); 6;63: 1079-1087.
4. Lieberman, J.A., "Comparative effectiveness of antipsychotic drugs: a commentary," Archives of General Psychiatry (October 2006); 6;63:1069-1072.
5. Rosenheck, R.A., "Outcomes, costs, and policy caution—a commentary on the cutlass study," *Archives of General Psychiatry* (October 2006); 6;63:1074-1076.
6. Stroup T.S., et al., "Effectiveness of olanzapine, quetiapine, risperidone, and ziprasidone in patients with chronic schizophrenia following discontinuation of a previous atypical antipsychotic." *American Journal of Psychiatry,* (April 2006);163(4):611-622.
7. McEvoy J.P., et al., "Effectiveness of clozapine vs. olanzapine, quetiapine, and risperidone in patients with chronic schizophrenia who did not respond to prior atypical antipsychotic treatment." *American Journal of Psychiatry,* (April 2006);163(4):600-610.
8. Davis, J.M., "The choice of drugs for schizophrenia," *New England Journal of Medicine,* (Feb. 2, 2006); 354(5): 518-520.
9. "Drugs for Psychiatric Disorders," Treatment Guidelines from the Medical Letter (June 2006); Vol. 4, No 46.
10. Carpenter, W.T. and Thaker, G.K., "Schizophrenia," *ACP Medicine* (June 2004); WebMD Inc.

11. "Guidance on the use of newer (atypical) antipsychotic drugs for the treatment of schizophrenia," Technical Appraisal Guidance # 43, National Institute for Clinical Excellence (NICE, England), May 2005, Update of June 2002 report. www.nice.org.uk.
12. "Which Atypical Antipsychotic for Schizophrenia," *Drugs and Therapeutics Bulletin* (August 2004); Vol. 42; No.8.
13. Schneider, M.S., et al., "Risk of death with atypical antipsychotic drug treatment for dementia," *JAMA* (Oct. 19, 2005): 294(15):1934-1943.
14. Wang, P.S., et al., "Risk of death in elderly users of conventional vs. atypical antipsychotic medications," *New England Journal of Medicine* (Dec. 1, 2005); 353(22):2335-2341.
15. Rabins, P.V. and Lyketsos,(no initials?) "Antipsychotic drugs in dementia," *JAMA* (Oct. 19, 2005), 294(15): 1963-1965.
16. Honer, W.G., et al., "Clozapine alone vs. clozapine and risperidone with refractory schizophrenia," *New England Journal of Medicine* (Feb. 2, 2006); 354(5):472-481.
17. "Second-generation Antipsychotics: Aripiprazole Revisted," *The Medical Letter* (Oct. 10, 2005); Vol. 47, Issue 1219.
18. Shekelle(no initials?), et al., *Off-Label Use of Atypical Antipsychotics—Draft Comparative Effectiveness Review* (November 2005). Agency for Healthcare Research and Quality. A review by the Effective Healthcare Program.
19. Schizophrenia, National Institute of Mental Health. Consumer booklet. 2005. www.nimh.nih.gov.
20. American Psychiatric Association. "Practice guidelines? for the treatment of patients with bipolar disorder," *American Journal of Psychiatry* (December 2004) 151 (Supplement).
21. Davidson M., Emsley R., Kramer M., et al., Efficacy, safety, and early response of paliperidone extended-release tablets (paliperidone ER): results of a six-week, randomized, placebo-controlled study. *Schizophrenia Research*. July 2007;93(1-3):117-130.
22. Kane J., Canas F., Kramer M., et al., Treatment of schizophrenia with paliperidone extended-release tablets: a six-week placebo-controlled trial. *Schizophrenia Research*. February 2007;90(1-3):147-161.
23. Conley, R. and(is someone missing here?) et al. (2005). "Risperidone, quetiapine, and fluphenazine in the treatment of patients with therapy-refractory schizophrenia." *Clinical Neuropharmacology* 28: 163-168.
24. Mullen, J., M. Reinstein, et al. (1999). "Quetiapine and risperidone in outpatients with psychotic disorders: results of the QUEST trial." E*uropean Neuropsychopharmacology* 9(Suppl 5): S267.
25. Potkin S.G., Gharabawi G.M., Greenspan A.J., et al., A double-blind comparison of risperidone, quetiapine and placebo in patients with schizophrenia experiencing an acute exacerbation requiring hospitalization. *Schizophrenia Research*. July 2006;85(1-3):254-265.
26. Zhong K.X., Sweitzer D.E., Hamer R.M., Lieberman J.A. Comparison of quetiapine and risperidone in the treatment of schizophrenia: A randomized, double-blind, flexible-dose, eight-week study. *Journal of Clinical Psychiatry*. July 2006;67(7):1093-1103.
27. Cutler A.J., Kalali A.H., Weiden P.J., Hamilton J., Wolfgang C.D. Four-week, double-blind, placebo- and ziprasidone-controlled trial of iloperidone in patients with acute exacerbations of schizophrenia. *J Clin Psychopharmacol*. April 2008;28(2 Suppl 1):S20-28.
28. Swartz M.S., Perkins D.O., Stroup T.S., et al., Effects of antipsychotic medications on psychosocial functioning in patients with chronic schizophrenia: findings from the NIMH CATIE study. *American Journal of Psychiatry*. March 2007;164(3):428-436.
29. Haro J.M., Novick D., Suarez D., et al., Remission and relapse in the outpatient care of schizophrenia: three-year results from the Schizophrenia Outpatient Health Outcomes study. *Journal of Clinical Psychopharmacology*. December 2006;26(6):571-578.
30. Dossenbach M.,, et? al., E.(is this initial supposed to be here?) Response and relapse in patients with schizophrenia treated with olanzapine, risperidone, quetiapine or haloperidol: 12-month follow-up of the Intercontinental Schizophrenia Outpatient Health Outcomes (IC-SOHO) study. *JournalClinical Psychiatry*. August 2005;66:1021-1030.
31. Swartz M.S., Perkins D.O., Stroup T.S., et al., Effects of antipsychotic medications on psychosocial functioning in patients with chronic schizophrenia: findings from the NIMH CATIE study. *American Journal of Psychiatry*. March 2007;164(3):428-436.