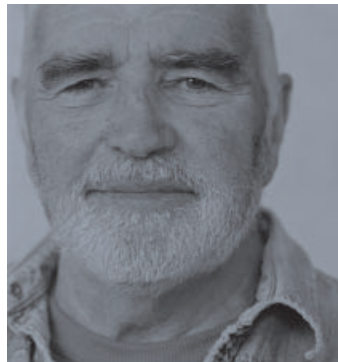
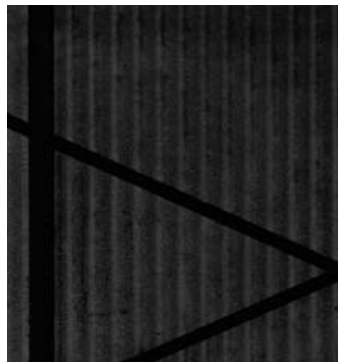


Consumer Reports BEST BUY DRUGS™

PROVEN • EFFECTIVE • AFFORDABLE



Treating Schizophrenia and Bipolar Disorder:
The Antipsychotics
Comparing Effectiveness, Safety, and Price



Our Recommendations

Antipsychotic drugs help many people with schizophrenia live more meaningful, stable lives with fewer - and sometimes no - periods of hospitalization.

But they are a highly problematic class of medicines. A sizeable percentage of people with schizophrenia get little or no benefit when they take an antipsychotic while others get only a partial reduction in symptoms. Side effects pose a major barrier to continuous use. In studies, 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 recent large-scale studies now indicate that, overall, the older drugs work just as well, at far lower cost.

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

The choice of generic perphenazine – if a patient responds well to it – saves about \$200 to \$500 a month (\$2,400 to \$6,000 a year) compared to Zyprexa and Risperdal, depending on the dose required.

We make no choice of a *Best Buy* antipsychotic for people with bipolar disorder. There is not enough evidence to do so.

This report was released and last updated in November 2006.

Welcome

This report evaluates a class of prescription medicines called antipsychotics. They are used primarily to treat people with schizophrenia. But they are also frequently prescribed to treat people with bipolar disorder (often called manic depression). The term “antipsychotic” refers to the fact that the drugs are used, in part, to reduce symptoms doctors generally call “psychotic,” such as hallucinations, delusions, disorganized thinking, and agitation. But 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 to www.CRBestBuyDrugs.org.

Some three million Americans have schizophrenia. It’s an illness that is still often mischaracterized in popular culture. People who have it do not have split personalities. Instead, they suffer from disjointed and illogical thinking. They may also be withdrawn, fearful and agitated, and experience hallucinations and delusions. 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 do live meaningful lives and function well with proper treatment.

What causes schizophrenia is unknown, though it has been clearly linked to biological abnormalities in the brain. Studies show it runs in families. It affects men and women about equally and occurs at similar rates in all countries and ethnic groups around the world. Men who are afflicted 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. As with schizophrenia, its cause is unknown and it can run in families. The hallmark symptoms are sharp swings between very high and very low moods – called mania and depression. In most cases, either mood lasts for several weeks and there is often an in-between period with a “normal” mood.

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 a third to half of people with bipolar disorder have a more severe form of it, with several episodes a year. The rest are less severely affected and may have months of stable mood 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).

Most of us understand the symptoms of depression pretty well – an overwhelming feel of sadness, hopelessness, and helplessness, and a loss of pleasure in life. But mania can be just as disturbing. It may be characterized at first by having boundless energy and feeling especially happy and creative. But this high mood often quickly spirals out of control. People with mania can turn 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 are prone to reckless, even destructive behavior.

The drugs analyzed in this report are used to treat the mania phase of bipolar disorder, but they are almost never the only drugs used to treat people with bipolar disorder. For example, the drug lithium is often prescribed for people with this disorder. Another is the anti-seizure medicine valproate (Depakote). People with bipolar disorder may also take antidepressants when in the depression phase of their illness.

This report focuses primarily on comparing the antipsychotic drugs developed in the past 15 years. These six 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. These older drugs are still used today and we discuss them in comparison to the newer ones. The antipsychotic drugs are:

Generic Name	Brand Name(s)	Available as a Generic?
Newer drugs		
Aripiprazole	Abilify	No
Clozapine	Clozaril	Yes
Olanzapine	Zyprexa, Zyprexa Zydis	No
Quetiapine	Seroquel	No
Risperidone	Risperdal, Risperdal M-Tab	No
Ziprasidone	Geodon	No
Older drugs*		
Chlorpromazine	Thorazine	Yes
Haloperidol	Haldol	Yes
Loxapine	Loxitane	Yes
Molindone	Moban	No
Perphenazine	Trilafon	Yes
Trifluoperazine	Stelazine, Suprazine	Yes
Thiothixene	Navane	Yes

*Selected older drugs. Does not present all that are available.

Note that clozapine is the only newer drug currently available as a generic. Risperidone (Risperdal) is scheduled to lose patent protection in 2007 or early 2008. All but one of the older antipsychotic medicines are available as generics.

Off-Label Use

Many of the drugs listed on the previous page are prescribed “off-label” to treat a range of other illnesses and conditions. The term off-label means that the drug is being prescribed for a use other than the one(s) approved by the Food and Drug Administration (FDA). This is not illegal in any way. Once a drug has been approved by the FDA, doctors can prescribe it in any way they see fit. Much off-label use is beneficial.

Antipsychotics are most often prescribed off-label to treat people with Alzheimer’s disease and stroke-related dementia. They are used to control agitation and aggression in people with these conditions. They are also sometimes used to treat people with obsessive-compulsive disorder, post-traumatic stress disorder, and personality disorder.

A recent analysis of over 100 studies of the off-label use of the newer antipsychotics, however, found mixed evidence for their effectiveness. Generally, they were no more or less effective than other drugs used to treat these conditions. In addition, there was inconsistent or little evidence that the drugs made any difference when added to other treatments – as a second or third drug, for example.

The treatment of people with Alzheimer’s disease (and other kinds of dementia) with antipsychotics deserves special mention. A study published in October 2005, which analyzed the results of 15 previous studies, found that Alzheimer’s disease and dementia patients given a newer antipsychotic had a higher risk of premature death (from stroke and other causes) compared to those not taking the drugs. A second major study published in October 2006 found that the side effects of the newer drugs offset their benefits in many people with Alzheimer’s disease. Yet a third recent study found that the older antipsychotic drugs, too, posed a higher risk of premature death among older people with dementia.

These research results have led to a wide-scale reassessment of the use of antipsychotics to treat people with Alzheimer’s disease or any form of dementia-related agitation and psychosis. For many such patients, the potential risks and harm from antipsychotics will outweigh the benefits.

The Older Drugs

The older drugs have been eclipsed in sales in the last decade by the newer ones because 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 groups of drugs, and the advantages of the newer drugs over the older ones can no longer be assumed.

The older drug we discuss most in this report is perphenazine. That's because it was compared in one major study to the newer drugs. 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 studies compare the older drugs to each other or to the newer drugs.

Prescription medicines are a mainstay of – and usually the first step in – the treatment of both schizophrenia and bipolar mania. 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 shows that a combined approach using psychosocial intervention and optimal drug treatment works best.

This report was released and last updated in November 2006.



What Are the Antipsychotics and Who Needs Them?

The antipsychotics are believed to work by affecting chemicals in the brain called neurotransmitters.

In general, almost everyone diagnosed with schizophrenia should be prescribed an antipsychotic when they are first diagnosed. For many, these drugs reduce symptoms and improve quality of life, as shown by dozens of studies dating back 40 years.

Indeed, some schizophrenics 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, the antipsychotics are far from a panacea in the treatment of this often debilitating disease. They don't significantly help a sizeable 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, in general, about half to 55 percent of 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 to 30 percent get a limited benefit.

The bar for "benefit" is also set quite low. Indeed, 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.

Importantly, people with schizophrenia are prone to periods of time in a hospital or 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 on their ability to "calm" mania symptoms. All the antipsychotics help in this regard, with 40 to 75 percent of 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 to 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 any given antipsychotic do not take it for long – even if it is reducing their symptoms – because they can not or do not wish to tolerate the side effects. In addition, people with schizophrenia and bipolar disorder are highly prone to quitting their medicine anyway 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 a bit. Cost can also be a factor.

Thus, while doctors are often at 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 to 90 percent of people who take an antipsychotic will have at least one side effect; most will have more than one. Of those who have any side effects:

- 20 to 30 percent will have a serious or intolerable adverse effect and stop taking the medicine within days, weeks, or a few months

- 35 to 45 percent will stop taking the medicine within six months, and
- 65 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 again with another drug is common and not always productive.

These results from studies beg the question of how best to use antipsychotics. These days, doctors will weigh a variety of factors before prescribing an antipsychotic, and choosing which one and at what dose. 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 also to persevere for a few

months through what can be a frustrating period when the drug does not seem to be helping 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 two or more antipsychotic medicines 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 be taking an antipsychotic even if the side effects are tough to tolerate. Extra efforts have to be made, by family and caregivers, to assure they stay on the drugs.
- People who have only mild symptoms or who are responding well to non-drug treatment should consider discontinuing their antipsychotic medicine if the side effects are outweighing the benefits.

Table 1. Antipsychotic Side Effects

Minor to severe – can ease or disappear over time, or be reduced if dose is lowered. They disappear when the drug is stopped. Not listed in any order of importance or severity. Most people have more than one of these effects. But experience and severity of side effects varies substantially.

- | | |
|---|--|
| <ul style="list-style-type: none"> • Abnormal muscle movements, tremors and spasms • Muscle weakness • Muscle stiffness • Lack of coordination • Restlessness • Dry mouth • Constipation • Sedation, drowsiness • Excessive salivation • Sensitivity to the sun | <ul style="list-style-type: none"> • Skin rashes • Blurred vision • Slurred speech • Rapid heartbeat • Insomnia • Dizziness when standing or moving quickly • Feeling more hungry than usual • Abnormal menstruation • Sexual dysfunction • Male infertility |
|---|--|

Not always so minor; may require discontinuing the drug; can in some cases become permanent.

- Tardive dyskinesia – characterized by uncontrollable body movement that may include tremors and spasms
- Significant weight gain (15 pounds and up)
- 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
- Seizures
- Agranulocytosis – failure of the bone marrow to produce disease-fighting white blood cells, which can lead to serious or fatal infections. (only with clozapine; regular blood tests required with use)
- Myocarditis – inflammation of the heart sack (only with clozapine)
- Neuroleptic Malignant Syndrome, characterized by high fever, increased heart rate, and blood pressure; can be fatal



- 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, heart disease, or who are obese, need to take special care in choosing an antipsychotic drug since several of the drugs increase the risk of these conditions more than others.

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 expensive. Recent years have seen a shift to these newer, costly drugs.

The problem is that the vast majority of people with schizophrenia are unemployed or only employed occasionally. Many lack health insurance and over half with insurance are covered in public programs such as Medicaid and Medicare (as disabled persons). Both these programs provide fairly open access to the newer drugs. As a result, the newer drugs cost these programs an estimated \$5 to \$7 billion per 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 in the next section starting with a less expensive older drug.

However, cost should never be the most important determinant of treatment. If a patient does not respond to an older antipsychotic, their 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 valproic acid, divalproex sodium (Depakote), and carbamazepine (Equetro) are also now widely used, and are proven effective. All are available as low-cost generic drugs.

For people in the throes of a severe manic episode, an antipsychotic is often prescribed along with lithium or valproate. After the symptoms are stabilized, doctors usually reassess the need for ongoing antipsychotic treatment and discontinue the antipsychotic medication unless it is required for control of 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

Unlike many classes of drugs, the newer antipsychotics have been compared to each other and to some of the older drugs in recent large-scale studies. These studies have helped clarify the strengths and weaknesses of each drug.

However, studies can never reveal whether or how much any individual will respond to a particular drug – what benefits or 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 a couple or even three medicines before finding one that works for them.

That said, research on the antipsychotics now provides solid guidance and cautions for anyone with a diagnosis of schizophrenia, and to a lesser extent those with bipolar disorder. There are four important things you need to know as you and a doctor, together, study the options.

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

(2) None of the antipsychotic drugs (other than clozapine) differ from each other in effectiveness

when all the research is considered, but the side effects and problems they can cause do differ – often substantially.

(3) Evidence is emerging that the newer drugs are no safer or less likely to cause side effects (including serious ones) than the older drugs. However, notably, some newer drugs cause fewer muscle and body movement problems in some patients.

(4) The newer drugs cost many times more than older ones. (See Table 4 on page 14)

Tables 2 and 3 on this page and the next compare the newer drugs and one older drug (perphenazine) to each other on a number of the important measures of patient response and side effects. The numbers come from recent large-scale studies on these drugs, and from analyses done by the Drug Effectiveness Review Project. (See page 17.) Both tables apply to treatment of people with schizophrenia, and not bipolar mania. You’ll see some differences in numbers on the same measures between the two tables. That’s because the two tables were derived from varying data and studies and the actual measures differ somewhat between the two.

Starting on the next page, we discuss each drug, in turn, based on information from recent studies.

Table 2. Antipsychotic Drugs Compared – I

Drug	Short-term Response Rates ¹	Short-term Rate of Stopping Medication ²	Longer-term Rate of Stopping Medication ³	Hospitalization rates for Recurrence of Symptoms ³
Aripiprazole (Abilify)	IE ⁴	37%	IE	IE
Clozapine (Clozaril)	54%	35%	IE	IE
Olanzapine (Zyprexa)	53%	37%	64%	11%
Quetiapine (Seroquel)	IE	IE	82%	20%
Risperidone (Risperdal)	50%	37%	74%	15%
Ziprasidone (Geodon)	55%	43%	79%	18%

1. Response is defined as 20 percent or more improvement in symptoms. This is a measure of the effectiveness. Percentages are from various studies that compare the drugs to each other and to placebo.

2. In less than 12 months

3. Over an 18-month period

4. IE =inadequate evidence available

Table 3. Antipsychotic Drugs Compared – II¹

Drug	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 (Generic)	75%	16%	25%	16%	12%	No	11%

1. The results presented in this table are based on one landmark study, called the Clinical Antipsychotic Trials of Intervention Effectiveness, or CATIE for short. CATIE is the most comprehensive study comparing the antipsychotics. The study 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 September 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 cessation of the drug right away.
3. Reflects only those who gained 7 percent or more of 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. Elevated prolactin 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.

Ziprasidone (Geodon). This drug had a higher rate of short-term discontinuation – at 43 percent compared to 37 percent or less for the other drugs. Geodon also 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 linked by the FDA to a risk of abnormalities in the electrical signals of the heart that can lead to heart rhythm disturbances, fainting, and even death. So far, no studies link Geodon to higher rates of these serious outcomes compared to other antipsychotics. Still, we consider Geodon a poor choice for initial treatment at this point, except perhaps for people who are significantly overweight.

Quetiapine (Seroquel). This drug had the highest rate of discontinuation and hospitalization for recur-

rence of symptoms. It also had the highest rate of treatment failure, at 28 percent, though this measure was not statistically significantly different than several of the other drugs. Along with Geodon, we consider Seroquel a poor choice for initial treatment. It has no apparent advantages over the other drugs.

Olanzapine (Zyprexa). This drug presents a distinctly mixed picture of pluses and minuses. It had the lowest rate of treatment failure, treatment drop-out, and hospitalization for worsening of condition. It also has the longest “treatment duration” – the length of time patients stay on the drug before quitting.

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 not a good choice for people who are already overweight or have heart disease or diabetes. It may also present a greater risk of side effects in people who are prone to these conditions. But for many people with schizophrenia, 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 one key study, fewer patients trying a second drug (after treatment failure on a first drug) discontinued Zyprexa (67%) compared to Seroquel (84%) and Geodon (77%).

Risperidone (Risperdal). This drug had the lowest rate of intolerable side effects – which usually lead to stopping the medicine right away. But long-term drop-out was about the same as with other drugs. It also had somewhat more discontinuations due to lack of effectiveness.

Risperdal is also the only newer antipsychotic known to pose a risk of abnormal elevation of prolactin, a pituitary hormone. Elevations in prolactin can lead to sexual and reproductive difficulties and breast enlargement in women and men. It can also cause irregular menstruation in women. We do not consider Risperdal a good initial choice for most people with schizophrenia.

Risperdal may be a better choice, however, for people who need to try another antipsychotic after failing to respond to a first one. In the same study cited above, fewer such patients discontinued Risperdal (64%) than Zyprexa (67%), Seroquel (84%), or Geodon (77%).

Clozapine (Clozaril, Fzacio). This drug was the first of the newer antipsychotics (1989) and the only one currently available as a generic. It performs well against the other drugs but is not a 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 four percent of patients taking clozapine have seizures. About one 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. Studies show it can benefit some of these patients, who are often referred to as “treatment-resistant.”

Indeed, several studies have found clozapine more effective at reducing symptoms and preventing hospitalization than any other antipsychotic in people who have failed on the other drugs. In one study, for example, 44 percent of people who switched to clozapine stayed on it for 18 months compared to 18 percent who switched to another newer antipsychotic. And, on average, patients stayed on clozapine for 10 months compared to just three months for the other drugs.

Aripiprazole (Abilify). This drug is the most recently approved newer antipsychotic (2002). It was not included in the recent 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 widely advertised to doctors and consumers recently for the treatment of bipolar mania. As stated earlier, regular or routine prescription 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. Abilify is too new a medicine to warrant recommending it as a good first or second choice in the treatment of schizophrenia.

Generic perphenazine. This is an older antipsychotic and has been prescribed to treat schizophrenia since the 1970s. It ranked roughly equally with the newer drugs in terms of effectiveness, treatment dropout, and most side effects. It was included in the major comparison study of the antipsychotic drugs chiefly because previous studies and reports from routine clinical use indicated it had a moderate risk of serious side effects compared to some other older antipsychotics. However, in that recent study people who took perphenazine did have more movement problems and tardive dyskinesia than people taking the other drugs.

These results for perphenazine surprised many doctors when they were first reported in 2005, after publication of the large study whose results are presented in Table 3. But they have been substantially supported by another important study published in October 2006. That study, done in England, compared what happened to people with schizophrenia taking older antipsychotics with those taking newer drugs.

Notably, all the people in the study were switching from a drug that had not succeeded in helping them. After one year, the patients taking both older and newer drugs fared about the same in terms of reduction of symptoms, side effects, discontinuation of their medicine, and overall quality of life.

Table 4 on the next page presents the costs for all the newer and selected older antipsychotics.

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

- *Generic perphenazine* – as initial treatment for people newly diagnosed with schizophrenia and for people with schizophrenia who have failed on a newer drug and whose doctors think perphenazine is worth a try. Patients taking perphenazine should be monitored closely for muscle tremors and spasms.
- *Olanzapine (Zyprexa)* – for certain people with schizophrenia who take perphenazine first and get no or minimal benefit and/or experience intolerable side effects. Zyprexa is not a good option for people who are overweight, have blood sugar abnormalities, diabetes, or heart disease.
- *Risperidone (Risperdal)* – for people with schizophrenia who take perphenazine first and get minimal benefit and/or experience intolerable side effects.
- *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.

We make no choice of a Best Buy antipsychotic for people with bipolar disorder. There is not enough evidence to do so.

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 tough to achieve.

In addition, because of their chemical nature and the broad spectrum of patient response, all the antipsychotics are prescribed in a wide range of doses to meet patients' individual needs. People are usually started 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 lots more, as you can see in Table 4.

Perphenazine is by far the least expensive of our *Best Buy* choices, costing \$68 to \$112 per month, depending on the dose needed. We choose perphenazine as a *Best Buy* because it is the only older drug that has been specifically compared to the others in a major U.S. study. We would note, however, that in the light of recent studies doctors may now be more willing to try other older antipsychotics. Many of them are inexpensive generics, costing less than perphenazine.

Our choice of Zyprexa and Risperdal was driven by the evidence presented on pages 10-12. They are expensive newer drugs. But overall, they are the two best choices, as specified, if perphenazine or another older drug does not work. Our choice of Risperdal is also based on the good chance that a less expensive generic version will become available in 2007 or 2008. Note also that both these drugs offer the convenience of once-a-day dosing at some dose strengths.

Clozapine at most doses is substantially less expensive than Zyprexa or Risperdal. This greatly benefits the narrow range of patients with severe symptoms who fail on other drugs. For many patients, clozapine may be a last best shot at symptom reduction.

The savings available from choosing generic perphenazine first is significant. If a patient responds well to this drug, they could save about \$200 to \$500 per month (\$2,400 to \$6,000 per year) compared to Zyprexa and Risperdal, depending on the dose required. As can also be gleaned from Table 4, other older antipsychotics may yield even greater savings compared to the expensive newer drugs.

Table 4. The Antipsychotic Drugs – Doses and Costs

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

	Generic Name and Dose	Brand Name ¹	Frequency of Use Per Day ²	Total Daily Dose	Average Monthly Cost ³
	Aripiprazole 10mg tablet	Abilify	One	10mg	\$481
	Aripiprazole 15mg tablet	Abilify	One	15mg	\$469
	Aripiprazole 20mg tablet	Abilify	One	20mg	\$661
	Aripiprazole 30mg tablet	Abilify	One	30mg	\$657
	<i>Chlorpromazine 25mg tablet</i>	Generic	One-Three	25mg-75mg	\$14-\$42
	<i>Chlorpromazine 50mg tablet</i>	Generic	One-Three	50mg-150mg	\$17-\$51
	<i>Chlorpromazine 100mg tablet</i>	Generic	One-Three	100mg-300mg	\$21-\$63
	<i>Chlorpromazine 200mg tablet</i>	Generic	One-Three	200mg-600mg	\$25-\$75
CR BEST BUY	Clozapine 25mg tablet	Generic	One-Three	25mg-75mg	\$37-\$111
CR BEST BUY	Clozapine 50mg tablet	Generic	One-Three	50mg-150mg	\$65-\$195
CR BEST BUY	Clozapine 100mg tablet	Generic	One-Three	100mg-300mg	\$172-\$516
CR BEST BUY	Clozapine 25mg dissolvable tablet	Fazaclo	One-Three	25mg-75mg	\$52-\$156
CR BEST BUY	Clozapine 100mg dissolvable tablet	Fazaclo	One-Three	100mg-300mg	\$127-\$381
	<i>Haloperidol 0.5mg tablet</i>	Generic	Three	1.5mg	\$27
	<i>Haloperidol 1mg tablet</i>	Generic	Two-Three	2mg-3mg	\$21-\$32
	<i>Haloperidol 2mg tablet</i>	Generic	Two-Three	4mg-6mg	\$27-\$41
	<i>Haloperidol 5mg tablet</i>	Generic	One-Three	5mg-15mg	\$21-\$62
	<i>Haloperidol 10mg tablet</i>	Generic	One-Two	10mg-20mg	\$38-\$76
	<i>Loxapine 10mg capsule</i>	Generic	Two-Three	20mg-30mg	\$72-\$108
	<i>Loxapine 25mg capsule</i>	Generic	One-Three	25mg-75mg	\$50-\$150
	<i>Loxapine 50mg capsule</i>	Generic	One-Three	50mg-150mg	\$70-\$210
CR BEST BUY	Olanzapine 5mg tablet	Zyprexa	One	5mg	\$275
	Olanzapine 5mg dissolvable tablet	Zyprexa Zydis	One	5mg	\$327
CR BEST BUY	Olanzapine 7.5mg tablet	Zyprexa	One	7.5mg	\$338
CR BEST BUY	Olanzapine 10mg tablet	Zyprexa	One	10mg	\$418
	Olanzapine 10mg dissolvable tablet	Zyprexa Zydis	One	10mg	\$494
CR BEST BUY	Olanzapine 15mg tablet	Zyprexa	One	15mg	\$629
	Olanzapine 15mg dissolvable tablet	Zyprexa Zydis	One	15mg	\$637
CR BEST BUY	Olanzapine 20mg tablet	Zyprexa	One	20mg	\$866
	Olanzapine 20mg dissolvable tablet	Zyprexa Zydis	One	20mg	\$868
	<i>Molindone 10mg tablet</i>	Moban	Two-Three	20mg-30mg	\$154-\$231
	<i>Molindone 25mg tablet</i>	Moban	One-Three	25mg-75mg	\$105-\$315
	<i>Molindone 50mg tablet</i>	Moban	One-Three	50mg-150mg	\$153-\$459
CR BEST BUY	Perphenazine 2mg tablet	Generic	Four	8mg	\$68
CR BEST BUY	Perphenazine 4mg tablet	Generic	Two-Four	8mg-16mg	\$48-\$96
CR BEST BUY	Perphenazine 8mg tablet	Generic	Two-Four	16mg-32mg	\$56-\$112

Table 4. The Antipsychotic Drugs – Doses and Costs

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

	Generic Name and Dose	Brand Name ¹	Frequency of Use Per Day ²	Total Daily Dose	Average Monthly Cost ³
CR BEST BUY	<i>Perphenazine 16mg tablet</i>	Generic	One-Two	16mg-32mg	\$39-\$78
	Quetiapine 25mg tablet	Seroquel	Two	50mg	\$152
	Quetiapine 50mg tablet	Seroquel	Two	100mg	\$256
	Quetiapine 100mg tablet	Seroquel	Two	200mg	\$266
	Quetiapine 200mg tablet	Seroquel	Two	400mg	\$502
	Quetiapine 300mg tablet	Seroquel	Two	600mg	\$662
	Quetiapine 400mg tablet	Seroquel	Two	800mg	\$782
CR BEST BUY	Risperidone 0.25mg tablet	Risperdal	Two	0.50mg	\$276
CR BEST BUY	Risperidone 0.5mg tablet	Risperdal	Two	1mg	\$298
	Risperidone 0.5mg dissolvable tablet	Risperdal	Two	1mg	\$336
CR BEST BUY	Risperidone 1mg tablet	Risperdal	Two	2mg	\$318
	Risperidone 1mg dissolvable tablet	Risperdal	Two	2mg	\$396
CR BEST BUY	Risperidone 2mg tablet	Risperdal	Two	4mg	\$520
	Risperidone 2mg dissolvable tablet	Risperdal	Two	4mg	\$638
CR BEST BUY	Risperidone 3mg tablet	Risperdal	One-Two	3mg-6mg	\$303-\$606
	Risperidone 3mg dissolvable tablet	Risperdal	One-Two	3mg-6mg	\$387-\$774
CR BEST BUY	Risperidone 4mg tablet	Risperdal	One	4mg	\$405
	Risperidone 4mg dissolvable tablet	Risperdal	One	4mg	\$500
	<i>Thiothixene 2mg capsule</i>	Generic	Two-Three	2mg-6mg	\$22-\$33
	<i>Thiothixene 5mg capsule</i>	Generic	One-Three	5mg-15mg	\$15-\$45
	<i>Thiothixene 10mg capsule</i>	Generic	One-Three	10mg-30mg	\$17-\$51
	<i>Trifluoperazine 2mg</i>	Generic	One-Three	2mg-6mg	\$19-\$57
	<i>Trifluoperazine 5mg</i>	Generic	One-Three	5mg-15mg	\$22-\$66
	<i>Trifluoperazine 10mg</i>	Generic	One-Two	10mg-20mg	\$34-\$68
	Ziprasidone 20mg capsule	Geodon	Two	40mg	\$386
	Ziprasidone 40mg capsule	Geodon	Two	80mg	\$398
	Ziprasidone 60mg capsule	Geodon	Two	120mg	\$406
	Ziprasidone 80mg capsule	Geodon	Two	160mg	\$408

1. For the first-generation drugs – whose 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. Over 90 percent of the prescriptions for these drugs are generic. For clozapine, only the generic prices are given for the oral, non-dissolvable tablet form.
2. Dose range recommendations for the second-generation antipsychotics are derived from the American Psychiatric Association Schizophrenia Reference Guide and The Medical Letter – Treatment Guidelines for Antipsychotic Drugs (June 2006, Issue 46). Dose ranges for the first-generation drugs are from Consumer Reports Consumer Drug Reference (2006 Edition) and The Medical Letter – Treatment Guidelines for Antipsychotic Drugs (June 2006, Issue 46). 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.
3. Prices reflect nationwide retail averages for September 2006; rounded to the nearest dollar. Information derived by *Consumer Reports Best Buy Drugs* from data provided by Wolters Kluwer Health, Pharmaceutical Audit Suite.

Talking With Your Doctor

It's important for you to know that the information we present in this report is not meant to substitute for a doctor's judgment. But we hope it will help a doctor and you arrive at a decision about whether you (or a family member) need an antipsychotic drug and, if so, which one is best.

Bear in mind that many people are reluctant to discuss the cost of medicines with their doctors 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 many physicians) also believe that newer drugs are always or almost always better. While that's a natural assumption to make, the fact is that it's not true (as the latest evidence on the antipsychotics indicates). Think of the older medicines as "tried and true." Newer drugs have not yet met the test of time, and unexpected problems can and do crop up once they hit 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 almost always 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 about half of all prescriptions in the U.S. are 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, they may not always tell each other which drugs have been prescribed for you.
- Second, it is very common for doctors today to prescribe several medicines for you before finding one that works well or best, mostly because people vary in their response to prescription drugs.
- Third, more and more people today take several prescription medications, nonprescription drugs and supplements all at the same time. Many of these interact in ways that can be very 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 list of the drugs you are taking, both prescription and nonprescription and including dietary supplements.

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 the 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 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 14-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/drugeffectiveness/reports/final.cfm>. (This is a long and technical document written for physicians.)

Our analysis also relied on the results of several major studies published in the last year or so. 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 September 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 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 healthcare information company which tracks the 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 September 2006.

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.CRBestBuyDrugs.org.

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.CRBestBuyDrugs.org.

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The first reference on this list is to the Drug Effectiveness Review Project Report on the antipsychotic drugs. This report was the main resource for our evaluation. It lists 463 references. We refer you to that report for a comprehensive list of studies and medical literature citations. The other references we list here are the principle sources of information used to produce this Consumer Reports Best Buy Drugs analysis of the antipsychotic medicines.

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