Consumer Reports

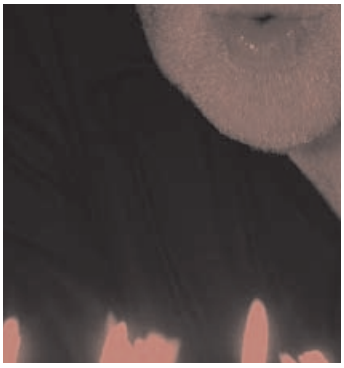
BEST BUY DRUGS™

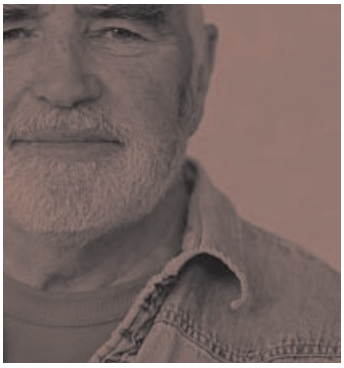
PROVEN • EFFECTIVE • AFFORDABLE

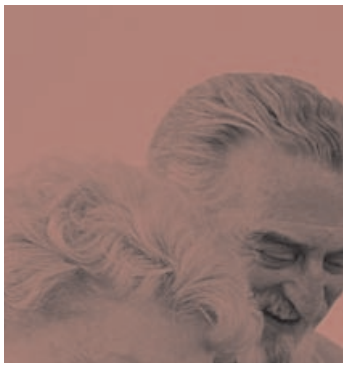
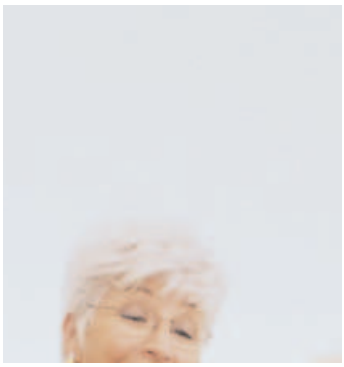
Evaluating Prescription Drugs Used to Treat:

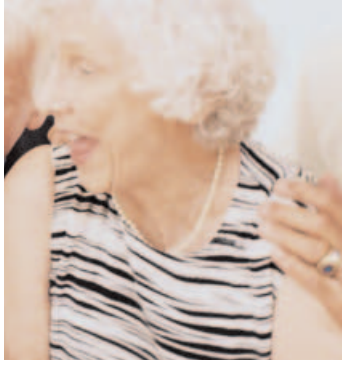
Alzheimer's Disease

Comparing Effectiveness, Safety, and Price





Our Recommendations

The medicines used to slow mental decline in people with Alzheimer's disease are not particularly effective. When compared to a placebo, only 10% to 20% more people taking an Alzheimer's drug seem to benefit at all. And it is the rare person who has a significant delay in the worsening of their symptoms over time.

However, there is no way as yet to predict who will respond and who will get little or no benefit from one of the five drugs approved to treat Alzheimer's disease. Thus, the decision to try one is a gamble and judgment based on whether the treatment is worth the cost and the risk of side effects.

- *Cost.* Averaging about $148 to $195 a month, the Alzheimer's disease drugs are costly and may not be worth it if the patient has to take many other medicines. This is true even if insurance or Medicare coverage helps pay since out-of-pocket payments can still be quite steep.

- *Side effects.* While the long-term adverse effects of the Alzheimer's drugs have not been fully evaluated, short-term side effects are either mild or reversible when a person stops taking the medicine. On this basis, many people with Alzheimer's disease may opt to try one of the drugs for six months to a year to see if it helps. We advise close scrutiny of the patient's response by both family and physician.

Based on the evidence of their effectiveness, side effects, tolerability, flexibility of use, and cost, we have chosen the following as *Consumer Reports Best Buy Drugs* to treat Alzheimer's disease:

- *Donepezil (Aricept)* – for people with early-stage Alzheimer's disease
- *Galantamine (Razadyne)* – for people with early-stage Alzheimer's disease
- *Memantine (Namenda)* – for people with middle-stage and late-stage Alzheimer's disease

Aricept's and Razadyne's lower risk of adverse effects and higher tolerability justify their choice. We choose Namenda because it is the only drug approved by the FDA to treat people with middle- to late-stage Alzheimer's disease. It also acts differently in the body than the other drugs and because of that can be taken in addition to them. That could be an advantage, but we caution that studies have not yet conclusively established whether such combination treatment is better than treatment with one drug alone.

Welcome

This report compares the effectiveness, safety, and cost of medications used to treat Alzheimer's disease. It is part of a Consumers Union and *Consumer Reports* project to help you find medicines that are safe and effective and 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, please go to www.CRBestBuyDrugs.org

Alzheimer's disease is the most common form of dementia, the medical term for a decline in memory, thinking, decision-making, and reasoning. It and other dementias affect about 8 million people in the U.S, including 40% to 50% of people age 85 and over. In 2004, an estimated 4.5 million people had Alzheimer's disease. That number is projected to almost triple to 13.2 million by 2050 as the baby boomers move into their senior years.

Despite years of research, no one knows exactly what causes the damage to brain cells, structure, and function that leads to Alzheimer's disease. Recent research indicates that your chance of developing Alzheimer's is strongly genetic – that is, it tends to run in families and you inherit a tendency to get it. However, that does not mean you will get it even if you have a family history of Alzheimer's. Studies suggest, for example, that regular physical and mental activity that keeps your mind engaged – such as doing crossword puzzles or playing bridge – as well as strong social ties and personal relationships, may help to prevent its onset.

People with high blood pressure, high cholesterol and diabetes may also be at increased risk for dementia. So, controlling those conditions with a healthy lifestyle and proper treatment may also help.

Many people, as they age, worry they might be developing Alzheimer's disease when they start forgetting simple things, such as phone numbers or the time of appointments, or when they start misplacing things such as keys and eye glasses. Those problems are common and usually do not indicate any memory or brain disorder, even when they get a little worse as you age. Actually, the symptoms of Alzheimer's are quite distinct. Table 1 on the next page gives you a quick assessment of the difference, and the various stages of Alzheimer's disease.

In the early stages, symptoms and behavioral changes may be quite mild and minimally disruptive. Or only a few symptoms may be present, such as short-term memory loss. This stage may last for up to a couple of years. But as time goes by, the symptoms usually worsen. As the disease progresses to the middle stages, a person may wander away from home, be unable to do even easy math or writing, have trouble getting dressed, and become delusional.

In the late stages of the disease, Alzheimer's patients usually can't communicate with words, forgets how to bathe, eat, dress or use the toilet, and may even lose the ability to swallow or chew. The personality changes also deepen, and some people with Alzheimer's become abusive, highly anxious, agitated, delusional, or paranoid. Alzheimer's is eventually a fatal disease although many of its victims die of something else, such as pneumonia, and not the dementia itself.

At any point in time, about half of the people with Alzheimer's have early-stage disease and the other half middle- or late stage-disease.

If you or a loved one has any of the symptoms listed in columns 2, 3 and 4 of Table 1, we would advise you to seek medical care as soon as possible.

Table 1. The Stages of Alzheimer's Disease

Not Alzheimer's	Early-stage	Middle-stage	Late-stage
■ Forgetting things occasionally ■ Misplacing items, like keys, eye glasses, bills, paper work ■ Forgetting the names or titles of some things, like movies, books, people's names ■ Some reduction in ability to recall words when speaking ■ Being "absent-minded" or sometimes hazy on details ■ "Spacing things out," such as appointments	■ Short-term memory loss, usually minor ■ Being unaware of the memory lapses ■ Some loss, usually minor, in ability to retain recently learned information ■ Forgetting things and unable to dredge them up, such as the name of a good friend or even family member ■ Function at home normally with minimal mental confusion, but may have problems at work or in social situations ■ Symptoms may not be noticeable to all but spouse or close relatives/friends	■ Short-term memory loss deepens, may begin to forget conversations completely or name of street where you live, names of loved ones or how to drive a car ■ Mental confusion deepens, trouble thinking logically ■ Some loss of self-awareness ■ Friends and family notice memory lapses ■ May become disoriented, not know where you are ■ Impaired ability to perform even simple arithmetic ■ May become more aggressive or passive ■ Difficulty sleeping ■ Depression	■ Severe cognitive impairment and short-term memory loss ■ Speech impairment ■ May repeat conversations over and over ■ May not know names of spouse, children, or caregivers, or what day or month it is ■ Very poor reasoning ability and judgment ■ Neglect of personal hygiene ■ Personality changes; may become abusive, highly anxious, agitated, delusional, or even paranoid ■ May need extensive assistance with activities of daily living

Sources: Multiple, including the Alzheimer's Association

Especially in its early stages, Alzheimer's is not easy to diagnose. A diagnosis usually involves a series of oral and written tests that evaluate memory and thinking ability. You may also be given blood or other tests to rule out other potential causes of dementia, such as Parkinson's disease or stroke (including mini-strokes called transient ischemic attacks, or TIAs), hypothyroidism, and vitamin B-12 deficiency (also called pernicious ane-

mia). In addition, many medicines can produce mental and behavioral changes that mimic the symptoms of dementia in older persons.

Based on your other medical problems, a doctor may also order radiological tests, such as a CT or MRI, to check for other causes of memory loss. But those tests at present are unable to determine conclusively if a person with memory loss has Alzheimer's disease or another form of dementia.

Differentiating older people who have depression versus early Alzheimer's can be a challenge, too. Depression occurs in up to half of people with Alzheimer's and may in fact be more pronounced in the early stages when people are grappling with the onset of the disease. But, of course, seniors without Alzheimer's can also become clinically depressed. Thus, it's important that an older person who is suspected of having Alzheimer's or depression receive thorough testing and a definitive diagnosis.

Five drugs are currently approved by the Food and Drug Administration (FDA) to specifically treat Alzheimer's disease. They are:

Generic Name	Brand Name(s)	Available as a Generic Drug?
Donepezil	Aricept	No
Galantamine	Razadyne (Reminyl)* Razadyne ER	No
Memantine	Namenda	No
Rivastigmine	Exelon	No
Tacrine	Cognex	No

* The brand name for galantamine was changed from Reminyl to Razadyne in April 2005 in the U.S. to avoid confusion with the diabetes drug Amaryl.

These five medicines are sometimes used to treat other conditions that can lead to dementia, such as Parkinson's disease. In this report, however, we focus on their use to treat people with Alzheimer's disease.

Although many have been tried, no other types of medicines have been shown effective in delaying the onset or reducing Alzheimer's symptoms and disabilities. This includes the anti-inflammatory drugs such as ibuprofen (Advil, Motrin) and celecoxib (Celebrex), the Parkinson's disease drug selegiline (Eldepryl), the cholesterol-lowering drugs known as statins, or a drug called piracetam.

Likewise, studies have yet to show conclusively that alternative treatments work to delay its onset or help reduce Alzheimer's symptoms. This includes folic acid supplements, the Chinese herb ginkgo biloba, the epilepsy drug carbamazepine (Carbetrol, Tegretol), and vitamin C. Studies of these and

other vitamins, herbs and supplements continue, however, and a few have yielded positive findings. For example, one large study found that vitamin E delayed the progression of early- and middle-stage Alzheimer's disease.

Female hormone drugs (estrogen and progestin) were once thought to lower the chances of memory decline and getting Alzheimer's. But several studies have found conclusively that hormone replacement therapy is actually associated with an *increased* risk of dementia (mostly stroke-related but possibly also Alzheimer's).

It's important for you to know that medicines are but one component in the care of people with Alzheimer's. Studies indicate that psychosocial support and non-medical treatment is just as important.

That said, doctors sometimes prescribe other medicines (than those we focus on in this report) to help control some of the behavioral problems that can occur in people with Alzheimer's. They may, for example, prescribe antidepressants, anti-anxiety, and antipsychotic drugs. Antidepressants and anti-anxiety drugs – used appropriately and judiciously – may be helpful. Antipsychotic drugs – such as risperidone (Risperdal), quetiapine (Seroquel), and olanzapine (Zyprexa), are sometimes prescribed to help ease severe agitation, aggressive outbursts, and hallucinations. They may be useful but come with risks, including a potential for weight gain and diabetes. Also, a study in 2005 found that they actually may slightly increase the risk of death in seniors with dementia. As a result, the FDA in April 2005 recommended that antipsychotic drugs be used with caution in older people with dementia and Alzheimer's disease.

This report is based on a systematic analysis of the medical evidence on the drugs used specifically to treat Alzheimer's disease. There's more information on page 14 and at www.CRBestBuyDrugs.org about how we conducted our analysis.

This report was released and last updated in March 2006.

What Are Alzheimer's Drugs and Who Needs Them?

Four of the five Alzheimer's drugs – donepezil (Aricept), galantamine (Razadyne), rivastigmine (Exelon), and tacrine (Cognex) – belong to the same class and essentially work the same way. They reduce the breakdown in the brain of a chemical called acetylcholine, which is a chemical messenger that transmits information from nerve cell to nerve cell. This effectively increases levels of acetylcholine in the brain, and may preserve brain function.

The fifth and most recently approved drug, memantine (Namenda), works differently. It blocks the actions of the neurotransmitter glutamate. Glutamate is needed for memory but too much of it is toxic to nerve cells and it appears that in people with Alzheimer's, there is too much of it (for unknown reasons).

None of these five drugs "cures" Alzheimer's disease. Instead, studies have found they can slow a person's mental decline and ease symptoms (especially forgetfulness and confusion).

However, all the studies indicate that when people taking any of the Alzheimer's medicines are compared to those taking a placebo, only 10% to 20% more people taking the drug get a significant, noticeable or sustained response. And it is the rare person who has a strong response, with marked improvement or a significant delay in the worsening of symptoms. By another measure, one team of researchers calculated that for every three to seven people taking an Alzheimer's drug, only one benefits at all. Unfortunately, there is no way as yet to predict who will respond and who will have little or no benefit.

(Notably, some studies indicate that the general health of elderly people who take these medicines does not decline as rapidly, an indication they may have benefits other than those assessed by tests of mental function and memory.)

Thus, the decision by a doctor, the Alzheimer's patient, and his or her loved ones, is whether the treatment is worth it. Balanced against risk (of adverse effects) the answer may be yes for most people. Balanced against cost, the answer may be no for some.

Strictly speaking, a person with Alzheimer's does not need to take one of these medicines in the same way that a person with heart disease needs – or is strongly urged – to take medicines that will very likely prolong their life and improve its quality. Or the same way you may need to take a pain reliever if you have arthritis.

Given the poor to modest benefits of these drugs, four factors may be used to assess whether treatment with one of them is desirable:

- Symptoms and level of desire to retain as much brain function as possible
- Comfort with the risk of side effects
- Comfort with taking the drugs over many years
- Cost of the drugs and insurance coverage

Taking these factors one by one:

Symptoms and desire. Strong motivation to maintain independence and brain function is likely to compel many newly diagnosed Alzheimer's patients to try one of the Alzheimer's drugs, at least for awhile. All of the drugs except memantine (Namenda) are indicated for early-stage patients (as soon as the disease is diagnosed), and they are considered to be most effective when given in the early stages. But if symptoms are mild or moderate, a response in the early stages may be hard to notice. Therefore, the gamble is that the drug will work to delay decline and worsening of symptoms, and that a strong response will occur. It may or may not; every person is different.

Also, as the disease progresses, people often seem to get less benefit from any of the Alzheimer's drugs. The benefit they may have experienced in the early stages appears to wane or disappear.

Side effects: With one exception, none of the Alzheimer's drugs has been shown to pose a clear risk of severe adverse side effects or reactions. The exception is tacrine (Cognex). In studies, as many as half of patients who took Cognex had abnormal liver functions. Because of this, Cognex is far less prescribed than the other drugs we discuss.

The four remaining drugs can cause side effects, however, and for some people these outweigh the sometimes limited benefits. (Table 2 on the next page lists the main possible side effects.) In the next section we discuss how

the drugs vary with respect to the side effects they cause. The relevant point here is that from 10% to 20% of people *stop taking an Alzheimer's drug because of side effects*. The effects do go away when one stops taking the drug, with no permanent damage.

Table 2: Possible Side Effects

Relatively Minor:
Usually go away in time or are short-lived

- Nausea
- Vomiting
- Diarrhea
- Headache
- Insomnia

Not so Minor:
Can be annoying or dangerous and should be reported to a doctor.

- Slow heartbeat
- Persistent dizziness
- Sudden or substantial weight loss
- Unusual weakness
- Lack of appetite
- Stomach pain
- Yellowing of the skin

Taking the drugs long-term: The benefits of the Alzheimer's drugs only occur while they are being taken. When the drugs are stopped, the "holding pattern" of mental function may cease and a decline may begin or there may be a sudden worsening. Thus, you may have to take an Alzheimer's drug for years to sustain a benefit. The trouble is that very few studies have examined the long-term effectiveness and safety of these medicines. Most of the studies assessed people's response for just six months, though a few have suggested the benefits may last one to three years.

While there is as yet no proof of long-term problems, some adverse effects could exist. For example, some researchers believe the Alzheimer's drugs might cause a slowed heart rate over time. This can cause dizziness and lead to falls – a potentially dangerous situation in someone who might already be unsteady on their feet. While the evidence so far indicates the heart rate reduction is minimal, more research is needed. There is also the complication that tens of thousands of older people have undiagnosed heart failure (also called congestive heart failure) and a slowed heart rate could be dangerous for these people. (Doctors usually but may not always assess this before prescribing an Alzheimer's drug.)

In addition, research indicates that, with the exception of Namenda, all the Alzheimer's drugs can increase the risk of stomach bleeding and ulcers when taken for a long time.

Cost and coverage: The Alzheimer's drugs are relatively expensive medicines (costing around $1,700 to $2,300 a year). What you'll pay will depend, of course, on your drug insurance coverage. The drugs are now covered under the new Medicare drug benefit program (Part D). But you could still end up paying quite a lot out of pocket for these medicines, due to co-payments and the structure of the new Medicare drug benefit.

Some Medicare health plans, for example, will help you pay for the deductible, co-payments and cost of your medicines if Medicare temporarily stops paying for them (as happens when you hit the "donut hole" after around $2,250 in total drug expenses). But if you have less generous coverage – for example if you are in a "standard" Medicare drug plan – you pay quite a bit more.

Indeed, for many Alzheimer's patients, their families, and doctors, the decision of whether to take an Alzheimer's drug may be based in part on the expense of the other drugs they need and the additional out-of-pocket cost of an Alzheimer's specific drug. Many Alzheimer's patients have other chronic conditions that require them to take other medicines. In addition, many may be taking an antidepressant or other drug to help ease their Alzheimer's symptoms. For low-income and middle-income Alzheimer's patients, the burden of the cost for other medicines may simply be too great to justify another drug with a high co-payment if there is only a marginal chance the drug will bring them any benefit.

Choosing an Alzheimer's Drug – Our *Best Buy* Picks

The five Alzheimer's drugs are roughly equivalent in their effectiveness, with inconclusive evidence that any one is more effective than any other. These drugs are also roughly equivalent in price. (See Table 3 on page 10). They do differ in the side effects they cause, however, and that will be one major criterion on which we base our choice of which is a *Best Buy*.

Of the five, tacrine (Cognex) is ruled out. Your doctor is unlikely to prescribe this drug because it has been linked to liver damage. Should it be recommended, we advise a thorough conversation with your doctor about the choice, and a second opinion.

As mentioned earlier, all of the Alzheimer's drugs except memantine (Namenda) are indicated for treatment early in the course of the disease. Namenda is the only drug specifically approved by the FDA for treatment of middle-stage and late-stage Alzheimer's, although the other medicines are also commonly prescribed for people with later-stage disease. (Namenda is not approved to treat early-stage Alzheimer's. Indeed, studies have not yet shown it effective for such patients.)

That means you and your doctor have a choice of three drugs intended for early use: donepezil (Aricept), galantamine (Razadyne), and rivastigmine (Exelon). Of these three, Exelon had the highest incidence of several side effects when compared to both placebo and in studies that compared it to the other two. For example, in one analysis, 20% of people taking Exelon had nausea and vomiting, compared to 13% of those taking Razadyne and 7% taking Aricept.

Likewise, people taking Exelon also had higher rates of weight loss and dizziness compared to those taking Razadyne or Aricept. Aricept had the lowest rate of both these side effects in several studies. It should be noted, however, that other analyses failed to find statistically significant side effect differences among these three drugs.

It is also notable that several key studies of Namenda either did not report or did not evaluate these side effects. However, recent advertisements for Namenda in medical journals note that 7% of people had dizziness versus 5% who took a placebo. Only 3% reported vomiting when taking Namenda.

An important measure of any drug is how often patients stop taking it because of side effects. Exelon rates lower on this criterion, too. In one study, 22% of patients stopped taking it compared to 11% of those taking Aricept. In comparisons of Aricept and Razadyne, more patients stopped taking Razadyne in one 12-week study, but an equal number (13%) stopped taking each drug in a year-long study.

Based on the evidence of their effectiveness, side effects, tolerability, flexibility of use, and cost, we have chosen the following as *Consumer Reports Best Buy Drugs* to treat Alzheimer's Disease:

- *Donepezil (Aricept)* – for people with early-stage Alzheimer's disease
- *Galantamine (Razadyne)* – for people with early-stage Alzheimer's disease
- *Memantine (Namenda)* – for people with middle-stage and late-stage Alzheimer's disease

Aricept's and Razadyne's apparent lower risk of adverse effects and higher tolerability justify their choice. But, again, we emphasize the effectiveness of those two drugs may be marginal in many people who try them.

The choice of Namenda is due to its FDA approval to treat people with middle- to late-stage Alzheimer's disease, and because it can be taken in addition to the other Alzheimer's drugs. That's because it works in your body differently than the other drugs, which cannot be taken together.

Thus, if you get some benefit from Aricept or Razadyne in the early stages, but that benefit starts to wane over time, Namenda could be taken alone or alongside these other medicines. Indeed, Namenda is most often prescribed today in combination with one of the other Alzheimer's drugs in people with middle to late stage disease. However, the benefit of taking two medicines remains theoretical since no conclusive studies to date have shown the combination bet-

ter than one drug alone as initial therapy. In addition, the combined treatment doubles the cost.

The choice of Namenda is also driven by several recent studies suggesting a benefit lasting up to a year. By comparison, studies of the other Alzheimer's medicines have generally lasted only six months.

Aricept, Razadyne, and Namenda – as with the other Alzheimer's medicines – are usually prescribed at the lowest dose available when you first begin taking them. That dose is then doubled after a few weeks or months, depending on how you are tolerating the drug. And if that additional dose is also well tolerated, the dose may be increased again.

Importantly, because all the Alzheimer's drugs except Namenda work in the same way, switching from one to another usually does not produce significantly different results. However, that said, some patients do respond better to one drug than another, or may tolerate one better than another.

Table 3 : Cost Comparison for Alzheimer's Disease Drugs

Generic Name and Dose	Brand Name	Frequency of Use per Day[1]	Average Monthly Cost[2]
CR BEST BUY Donepezil tablet 5mg	Aricept	One	$160
CR BEST BUY Donepezil tablet 10mg	Aricept	One	$161
CR BEST BUY Galantamine tablet 4mg	Razadyne (Reminyl)[3]	Two	$177
CR BEST BUY Galantamine tablet 8mg	Razadyne (Reminyl)[3]	Two	$171
CR BEST BUY Galantamine tablet 12mg	Razadyne (Reminyl)[3]	Two	$176
CR BEST BUY Galantamine sustained release capsule 8mg	Razadyne ER	One	$181
CR BEST BUY Galantamine sustained release capsule 16mg	Razadyne ER	One	$178
CR BEST BUY Galantamine sustained release capsule 24mg	Razadyne ER	One	$178
CR BEST BUY Memantine tablet 5mg	Namenda	Two	$155
CR BEST BUY Memantine tablet 10mg	Namenda	Two	$148
Rivastigmine capsule 1.5mg	Exelon	Two	$188
Rivastigmine capsule 3mg	Exelon	Two	$193
Rivastigmine capsule 4.5mg	Exelon	Two	$191
Rivastigmine capsule 6mg	Exelon	Two	$189
Tacrine capsule 10mg	Cognex	Four	$353[4]
Tacrine capsule 40mg	Cognex	Four	$174[4]

(1) Frequency of use reflects typical dosing; some products may be used more or less frequently.
(2) Prices reflect nationwide retail average for October 2005, rounded to the nearest dollar. Information derived by *Consumer Reports Best Buy Drugs* from data provided by Wolters Kluwer Health, Pharmaceutical Audit Suite.
(3) Brand name for galantamine was changed from Reminyl to Razadyne in April 2005 in the U.S. to avoid name confusion with the diabetes drug Amaryl.
(4) Monthly cost based on less than 10 prescriptions.

The Evidence

This section presents more information on the effectiveness and safety of the drugs used to treat Alzheimer's disease.

This report is based primarily on an analysis of the available scientific evidence on Alzheimer's drugs. Overall, 1,035 studies and research articles were identified and screened. From these, the analysis focused on 38 high-quality studies that provided evidence of effectiveness or safety for the Alzheimer's drugs.

The benefits of these drugs are usually assessed based on the following criteria:

- Cognitive ability (e.g., memory, focus, reaction speed, etc.)
- Global response to treatment as assessed by a clinician or caregiver
- Daily functioning
- Behavior
- Quality of life

All five drugs have been shown to improve cognitive ability, but usually only slightly. All have also been found to generally improve a patient's overall response to treatment – both non-drug and using a variety of medicines to control or ease symptoms (such as antidepressants or anti-anxiety drugs).

Our analysis found inconsistent evidence on how these drugs compare in their ability to improve patients' daily functioning, behavior, or quality of life. A few of the drugs have been studied more extensively than others in these areas. Unfortunately, few studies directly and comprehensively compared one drug to another, which leaves open the question of whether any one is superior in effectiveness to the others.

Cognitive Ability

Most of the evidence, however, suggests that there's no substantial difference among the five drugs in their ability to produce improvements in memory and other cognitive functions. Compared to placebo, all five are capable of yielding noticeable changes in cognitive ability two to six weeks after treatment starts.

But, as stated earlier, only 10-20% more people who take the medications, versus those who take a placebo, can expect a significant improvement in cognitive ability.

Global Response

To assess whether patients are improving overall -- known as global response to treatment -- studies rely on the opinions of the treating physician and the caregiver, often a family member.

In general, all of the Alzheimer's medicines have been shown to improve a patient's well-being. However, not all patients will have this improvement. Studies have shown that around 10% of patients are considered to be "better" when assessed by their doctor or caregiver. Although others may not decline as much as they would have without drug treatment, overall improvement likely will not be noted for most patients.

There were no high quality studies comparing the different treatments head-to-head in their ability to improve overall well-being. Several studies evaluated physician and caregiver satisfaction with a drug when compared with another. Two compared donepezil (Aricept) to galantamine (Razadyne), and one compared Aricept to rivastigmine (Exelon). In two of these studies, Aricept performed somewhat better.

Daily Functioning

Daily functioning refers to the ability to perform normal activities of daily living, such as getting dressed, preparing food, shopping, housekeeping, or handling money. In the early stages of the disease, it is more difficult to determine whether a treatment can significantly affect these abilities. But as the disease progresses, this measure become more useful in assessing a drug's impact.

Daily functioning has not been measured in every study. And studies where it has been used have produced inconsistent results, partly because improvement can vary so much among people.

For example, Aricept was found to improve daily functioning in two studies but not in three others; three Razadyne studies found improvement in daily

functioning while two others did not. And in one year-long study comparing these two drugs, there was no difference between them.

Behavior

Evaluation of behavior may be more relevant in people with severe Alzheimer's disease, and since most of the drugs have been studied in earlier stages of the illness, behavior was not always measured.

The drugs' impact on behavior was assessed in seven studies: four with Aricept, two with Razadyne, and one with Namenda. Compared to no treatment, these drugs produced only minimal improvements. There was only one study that compared two drugs' effects on patients' behavior. In that year-long trial, there was no significant difference between Aricept and Razadyne.

Quality of life

There is scant evidence that the Alzheimer's drugs improve patients' quality of life. Seven studies – six of Aricept and one of Cognex – compared those drugs to placebo. Aricept appeared to significantly improve patients' quality of life in two of the studies, but they only lasted 12 to 15 weeks. There are no studies that compare one drug to another in the area of quality of life.

Drug Interactions

Although Alzheimer's drugs are generally safe, they may interact with other medicines or dietary supplements in ways that can be dangerous. Be sure to tell your doctor about all the other medications you are taking, including all vitamins and herbal therapies.

The main drugs to be concerned about are:

- Aspirin and NSAIDs. They increase the risk of stomach bleeding and ulcers, adding to a possible heightened risk posed by the Alzheimer's drugs (except Namenda)
- Anti-fungal medications, such as ketoconazole; they may increase the blood level of some Alzheimer's drugs, which could lead to more serious side effects
- Cimetidine (Tagamet), a medication used to treat heartburn; it may increase blood levels of some Alzheimer's drugs
- Certain antibiotics, such as erythromycin; they may increase blood levels of certain Alzheimer's drugs
- Certain medications used to treat depression, such as paroxetine (Paxil); they may increase Alzheimer's drug levels in the blood.
- Medications used to improve breathing, such as theophylline; this combination may cause dangerous side effects

It may occasionally be acceptable to take some of the medications together. Your doctor or pharmacist can tell you when combining the medications is appropriate or safe.

Certain other medications may interact with Alzheimer's drugs. Make sure to ask your doctor or pharmacist before taking any new prescription or over-the-counter medications.

Age, Race, and Gender Differences

Most Alzheimer's drug studies have been conducted in people who are 70-to-75 years old. Although some studies have tested Alzheimer's drugs in older people or more critically ill people who live in nursing homes, none has been able to determine if age makes a difference in how well the drugs work or if they are more or less safe.

No direct evidence suggests that any Alzheimer's drug has better or worse efficacy for any gender or racial group.

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 your doctor and you arrive at a decision about whether you need an Alzheimer's drug and, if so, which one is best for you.

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. 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 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 for Alzheimer's Disease

Our evaluation is primarily based on an independent scientific review of the evidence on the effectiveness, safety and adverse effects of the Alzheimer's drugs. A team of physicians and researchers at Oregon Health & Science University Evidence-based Practice Center conducted the analysis 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 Alzheimer's 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 Alzheimer's drugs is available at http://www.ohsu.edu/drugeffectivness/reports/final.cfm. (This is a long and technical document written for physicians.)

Our analysis also took into account an evaluation condcuted in March 2004 by the Deprtment of Veteran's Affairs Pharmacy Benefits Management Strategic Health Group. This can be obtained at www.vapbm.org. Our general advice on Alzheimer's disease diagnosis and treatment is also based on recent published reports and reputable online sources, including www.ConsumerReportsMedicalGuide.org, a new subscription Web site sponsored by Consumers Union and *Consumer Reports*.

The drug 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, even within a single city or town. All the prices in this report are national averages based on sales of prescription drugs in retail outlets. They reflect the cash price paid for a month's supply of each drug in October 2005.

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

- Be approved by the FDA for treating Alzheimer's disease.
- Have a safety record equal to or better than other Alzheimer's drugs.
- Have an average price for a 30-day supply that was not higher than the other Alzheimer's drugs.

The *Consumers Reports Best Buy Drugs* methodology is described in more detail in the Methods section at www.CRBestBuyDrugs.org.

About Us

Consumers Union, publisher of *Consumer Reports* magazine, is an independent and non-profit organization whose mission since 1936 has been to provide consumers with unbiased information on goods and services and to create a fair marketplace. It is solely responsible for the content of this report. Its main Web sites are www.consumersunion.org and www.consumerreports.org.

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.

We followed a rigorous editorial process to ensure that the information in this report and on the *Consumer Reports Best Buy Drugs* Web site is accurate and describes generally accepted clinical practices. If we find, or are alerted to, an error we will correct this as soon as possible. However, *Consumer Reports* and its authors, editors, publishers, licensors and any suppliers cannot be responsible for medical errors or omissions, or any consequences from the use of the information on this site. Please refer to our user agreement at www.CRBestBuyDrugs.org for further information.

Consumer Reports Best Buy Drugs should not be viewed as a substitute for a consultation with a medical or health professional. This report and the information on www.CRBestBuyDrugs.org are provided to enhance communication with your doctor rather than to replace it.

Sharing this Report

References

1. Peterson, Ronald (editor), *Mayo Clinic on Alzheimers Disease* (2002); Mayo Clinic Health Information, Rochester, MN/Kensington Publishing Corp, NY.
2. Molloy, W. & Caldwell, P., *Alzheimer's Disease: Everything You Need to Know – Revised Edition* (2003); Firefly Books, Buffalo, NY
3. Qizilbash N, Birks J, Lopez Arrieta J, Lewington S, Szeto S. Tacrine for Alzheimer's disease. *Cochrane Database Syst Rev* 2000; (3):CD000202.
4. Wilcock G, Howe I, Coles H et al. A long-term comparison of galantamine and donepezil in the treatment of Alzheimer's disease. *Drugs Aging* 2003; 20(10):777-89.
5. Jones R, Soininen H, Hager K et al. A multinational, randomised, 12-week study comparing the effects of donepezil and galantamine in patients with mild to moderate Alzheimer's disease. *Int J Geriatr Psychiatry* 2004; 19(1):58-67.
6. Wilkinson D, Passmore A, Bullock R et al. A multinational, randomised, 12-week, comparative study of donepezil and rivastigmine in patients with mild to moderate Alzheimer's disease. *Int J Clin Pract* 2002; 56(6):441-6.
7. Lanctot K, Herrmann N, Yau K et al. Efficacy and safety of cholinesterase inhibitors in Alzheimer's disease: a meta-analysis. *CMAJ* 2003; 169(6):557-64.
8. Birks J, Harvey R. Donepezil for dementia due to Alzheimer's disease. *Cochrane Database Syst Rev* 2004; (3):CD001190.
9. Whitehead A, Perdomo C, Pratt RD, Birks J, Wilcock GK, Evans JG. Donepezil for the symptomatic treatment of patients with mild to moderate Alzheimer's disease: a meta-analysis of individual patient data from randomised controlled trials. *Int J Geriatr Psychiatry* 2004; 19(7):624-33.
10. Olin J, Schneider L. Galantamine for Alzheimer's disease. *Cochrane Database Syst Rev* 2004; (3):CD001747.
11. Birks J, Grimley Evans J, Iakovidou V, Tsolaki M. Rivastigmine for Alzheimer's disease. *Cochrane Database Syst Rev* 2004; (4):CD001191.
12. Schneider L. AD2000: donepezil in Alzheimer's disease. *Lancet* 2004; 363(9427):2100-1.
13. Burns A, Rossor M, Hecker J et al. The effects of donepezil in Alzheimer's disease - results from a multinational trial. *Dement Geriatr Cogn Disord* 1999; 10(3):237-44.
14. Feldman H, Gauthier S, Hecker J, Vellas B, Subbiah P, Whalen E . A 24-week, randomized, double-blind study of donepezil in moderate to severe Alzheimer's disease. *Neurology* 2001; 57(4):613-20.
15. Homma A, Takeda M, Imai Y et al. Clinical efficacy and safety of donepezil on cognitive and global function in patients with Alzheimer's disease. A 24-week, multicenter, double-blind, placebo-controlled study in Japan. E2020 Study Group. *Dement Geriatr Cogn Disord* 2000; 11(6):299-313.
16. Mohs R, Doody R, Morris J et al. A 1-year, placebo-controlled preservation of function survival study of donepezil in AD patients. *Neurology* 2001; 57(3):481-8.
17. Rogers S, Doody R, Mohs R, Friedhoff L. Donepezil improves cognition and global function in Alzheimer disease: a 15-week, double-blind, placebo-controlled study. Donepezil Study Group. *Arch Intern Med* 1998; 158(9):1021-31.
18. Rogers S, Farlow M, Doody R, Mohs R, Friedhoff L. A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease. Donepezil Study Group.[see comment]. *Neurology* 1998; 50(1):136-45.
19. Rogers S, Friedhoff L. The efficacy and safety of donepezil in patients with Alzheimer's disease: results of a US Multicentre, Randomized, Double-Blind, Placebo-Controlled Trial. The Donepezil Study Group. *Dementia* 1996; 7(6):293-303.
20. Tariot P, Cummings J, Katz I et al. A randomized, double-blind, placebo-controlled study of the efficacy and safety of donepezil in patients with Alzheimer's disease in the nursing home setting. *J Am Geriatr Soc* 2001; 49(12):1590-9.
22. Winblad B, Engedal K, Soininen H et al. A 1-year, randomized, placebo-controlled study of donepezil in patients with mild to moderate AD. *Neurology* 2001; 57(3):489-95.
23. Raskind M, Peskind E, Wessel T, Yuan W. Galantamine in AD: A 6-month randomized, placebo-controlled trial with a 6-month extension. The Galantamine USA-1 Study Group. *Neurology* 2000; 54(12):2261-8.
24. Tariot P, Solomon P, Morris J, Kershaw P, Lilienfeld S, Ding C. A 5-month, randomized, placebo-controlled trial of galantamine in AD. The Galantamine USA-10 Study Group. *Neurology* 2000; 54(12):2269-76.
25. Wilcock G, Lilienfeld S, Gaens E. Efficacy and safety of galantamine in patients with mild to moderate Alzheimer's disease: multicentre randomised controlled trial. Galantamine International-1 Study Group. *BMJ* 2000; 321(7274):1445-9.
26. Corey-Bloom J, Anand J, Veach J, and E7BSG. A randomized trial evaluating the efficacy and safety of ENA 713 (rivastigmine tartrate), a new acetylcholinesterase inhibitor, in patients with mild to moderately severe Alzheimer's disease. *International Journal of Geriatric Psychopharmacology* 1998; 1:55-65.
27. Agid Y, Dubois B, Anand R, Gharabawi G. Efficacy and tolerability of rivastigmine in patients with dementia of the Alzheimer type. *Current Therapeutic Research, Clinical & Experimental* 1998; 59(12):837-45.
28. Rosler M, Anand R, Cicin-Sain A et al. Efficacy and safety of rivastigmine in patients with Alzheimer's disease: international randomised controlled trial. *BMJ* 1999; 318(7184):633-8.
29. Farlow M, Gracon S, Hershey L, Lewis K, Sadowsky C, Dolan-Ureno J. A controlled trial of tacrine in Alzheimer's disease. The Tacrine Study Group. *JAMA* 1992; 268(18):2523-9.
30. Reisberg B, Doody R, Stoffler A, Schmitt F, Ferris S, Mobius H. Memantine in moderate-to-severe Alzheimer's disease. *N Engl J Med* 2003; 348(14):1333-41.
31. Tariot P, Farlow M, Grossberg G, Graham S, McDonald S, Gergel I. Memantine

treatment in patients with moderate to severe Alzheimer disease already receiving donepezil: a randomized controlled trial. *JAMA* 2004; 291(3):317-24.
32. Wood P, Castleden C. A double-blind, placebo controlled, multicentre study of tacrine for Alzheimer's disease. Int. J Geriatr. Psych 1994; 9(8):649-54.
33. Areosa S, Sherriff F. Memantine for dementia. *Cochrane Database Syst Rev* 2004; (1):CD003154.
34. Potkin S, Anand R, Hartman R, Veach J, Grossberg G. Impact of Alzheimer's disease and rivastigmine treatment on activities of daily living over the course of mild to moderately severe disease. *Prog Neuropsychopharmacol Biol Psychiatry* 2002; 26(4):713-20.
35. Burns A, Spiegel R, Quarg P. Efficacy of rivastigmine in subjects with moderately severe Alzheimer's disease. *Int J Geriatr Psych.* 2004; 19(3):243-9.
36. Watkins P, Zimmerman H, Knapp M, Gracon S, Lewis K. Hepatotoxic effects of tacrine administration in patients with Alzheimer's disease. *JAMA* 1994; 271(13):992-8.
37. Dunn N, Pearce G, Shakir S. Adverse effects associated with the use of donepezil in general practice in England. *J Psychopharmacol* 2000; 14(4):406-8.
38. Knapp M, Knopman D, Solomon P, Pendlebury W, Davis C, Gracon S. A 30-week randomized controlled trial of high-dose tacrine in patients with Alzheimer's disease. The Tacrine Study Group. *JAMA* 1994; 271(13):985-91.
39. Farlow M, Brashear A, Hui S, Schneider L, Unverzagt F, and TSG. The effects of tacrine in patients with mild versus moderate stage Alzheimer's disease. *Research Advances in Alzheimer's Disease and Related Disorders* 1995; 283-92.
40. Knopman D, Schneider L, Davis K et al. Long-term tacrine (Cognex) treatment: effects on nursing home placement and mortality, Tacrine Study Group. *Neurology* 1996; 47(1):166-77.