

JOHNS HOPKINS GUIDE TO ANTIDEPRESSANTS
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Introduction

Antidepressant medication is the most common form of therapy for depression. The medications currently available work in a variety of ways depending upon the class of drug chosen.

We now have more treatment choices than ever before, and also more clinical evidence regarding the effectiveness of these treatments thanks to the STAR*D study, which will be summarized below.

How Antidepressants Work

Antidepressants affect levels of neurotransmitters—chemical messengers in the brain that facilitate communication between nerve cells.

Classes Of Medications Available

These days, physicians can choose from a growing number of antidepressant drugs from various drug classes, including:

selective serotonin reuptake inhibitors (SSRIs)
tricyclics
tetracyclics
dopamine reuptake inhibitors,
serotonin and norepinephrine reuptake inhibitors
and monoamine oxidase (MAO) inhibitors.

They will each be discussed in turn starting on page 7.

Finding The Right Drug Regimen

Because of this wide variety of antidepressants currently available, it isn't always easy to find a drug regimen that works for a particular individual.

Most people suffering from depression do get somewhat better with antidepressant medication, but relatively few people get completely better with the first drug they try.

But thanks to the findings of the STAR*D study on persistent depression, which was undertaken over a 7-year period, we now have more evidence-based guidance on optimal next-step strategies if patients don't get relief from the first drug they try.

The STAR*D Findings On Antidepressants

The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial is a recent landmark study on antidepressants funded by the National Institute of Mental Health. Its final results of all four levels of the study were published recently and summarized by our specialists in the April 6th, 2007 (Spring 2007) issue of *The Johns Hopkins Depression and Anxiety Bulletin*.

The findings of the STAR*D study conclude: If you're on an antidepressant and it's not working, don't give up on it. You may need a higher dose, a longer duration of therapy, a different drug altogether, or a combination of medications.

The STAR*D researchers found that systematically trying these treatment options can lead not just to a reduction in symptoms, but even to a remission in symptoms in up to half of severely depressed patients.

The Advantages Of Treatment With Antidepressants

There are several advantages to treating depression with medications:

- They are effective against mild, moderate, and severe depression.
- People usually respond more quickly to drugs than to psychotherapy.
- They are easy to administer.
- They are not addictive and, *when properly used*, are relatively safe.
- They can be used in combination with psychotherapy.

The Disadvantages Of Treatment With Antidepressants

The disadvantages to treating depression with medications are:

- Drug therapy can cause unwanted side effects.
- It requires strict adherence to a medication schedule.
- They can be dangerous if improperly used.
- They can be dangerous if a person does not inform their doctor of all the over-the-counter and herbal remedies they might be taking.

- It may take some time—and some adjustments—to find the right medication at the right dose. Physicians cannot predetermine which medication will be the most effective in a person. Drug selection relies largely on a process of educated guesses, and on the patient adhering to their medication schedule.

Choosing The Right Antidepressant

You will need to work with your doctor to find the right treatment for you, based on a number of short-term and long-term considerations.

Avoiding Unwanted Side Effects

For a person with a first-time episode of moderate-to-severe depression, the choice of medication is typically based on avoidance of side effects and drug interactions.

As an example, the tricyclic antidepressant amitriptyline (Elavil) can lower blood pressure and cause drowsiness and confusion—side effects that make it an inappropriate choice for many older people.

It is important to discuss with your doctor your concerns about unwanted side effects, including sexual side effects or unwanted weight gain.

Length Of Time Until Improvement of Symptoms

By themselves, antidepressant drugs can produce a significant improvement in four to six weeks, although it may take up to 12 weeks on a therapeutic dose to see the full benefit of the medication chosen.

The Maintenance Phase

If a person responds fully to medication after this period, treatment moves on to the continuation/maintenance phase, which typically lasts at least six months to a year at the same dosage level.

When A Drug Does Not Give Enough Relief

When a drug does not work, a doctor may prescribe an antidepressant from another class of medications, because drugs in other classes work differently.

Different Classes Of Drugs Have Different Side Effects

When a drug from one class is producing good results but causes unacceptable side effects, switching to a different medication within the same class can often help.

In 20%–50% of patients, adding the drug lithium can help boost the action of an antidepressant. However, lithium increases the risk of side effects and adverse drug interactions, requiring close monitoring by a physician.

Discontinuing A Drug after Successful Treatment

After successful treatment, when maintenance therapy is no longer needed, drugs are discontinued slowly over a period of one to three weeks to avoid withdrawal symptoms.

Continual Monitoring By Your Doctor

Relapses are most common during the first two months after a person stops taking an antidepressant. It is therefore important for individuals to remain in contact with their physicians during this period. Should a relapse occur, a drug that was used successfully the first time often proves effective again.

Length Of Time For Treatment Of Depression

When it comes to the length of treatment for depression, there is no “one size fits all.” Generally, people require a year or more of treatment with antidepressant medication to treat an episode of major depression adequately. People with severe or recurring depression may require much longer treatment periods. Some people even remain on antidepressants for life.

The Importance Of Taking Your Antidepressants As Prescribed

A word of caution regarding the importance of taking antidepressant medication as prescribed: Antidepressants are the fourth leading cause of drug overdose, and the third leading cause of drug-related death when taken improperly.

Differing Responses To Antidepressants Due To Age

Older people are more susceptible to the adverse effects of antidepressants than younger people, so drug therapy must be approached carefully. Lower doses and closer monitoring for adverse effects and drug interactions are often required. But older patients may not have the support network or financial resources for the close monitoring required to fine-tune their treatment.

Ensuring that the drugs are being taken as prescribed is another concern. Moreover, since depression often accompanies physical illness in the older person, it is likely they will already be taking medications which might interact with their antidepressants.

In addition, when a person with latent bipolar disorder starts taking antidepressants, manic symptoms may develop and require treatment.

The Different Classes Of Drugs Available

Physicians can choose from a growing number of antidepressant drugs from various drug classes, including:

selective serotonin reuptake inhibitors (SSRIs)
tricyclics
tetracyclics
dopamine reuptake inhibitors,
serotonin and norepinephrine reuptake inhibitors
and monoamine oxidase (MAO) inhibitors.

They will each be discussed in turn.

Selective Serotonin Reuptake Inhibitors (SSRIS)

Low levels of the neurotransmitter serotonin have been linked to depression.

SSRIs, such as citalopram (Celexa), fluoxetine (Prozac), fluvoxamine (Luvox), paroxetine (Paxil), and sertraline (Zoloft), and the newest drug escitalopram (Lexapro) increase levels of serotonin in the brain. All of the SSRIs have similar rates of effectiveness and similar side effects, although it is possible that an individual might respond better or experience fewer side effects with a particular SSRI.

Because SSRIs have milder side effects than other antidepressants, most doctors now consider them the first-line drug treatment for depression. Studies have demonstrated that SSRIs are as effective as tricyclics, but advantages of SSRIs over tricyclics include a lower risk of fatal overdoses and serious heart rhythm disturbances in people with cardiac disease.

The STAR*D study states that 30% of patients achieve remission with the first medication prescribed. And that switching from one SSRI is almost as effective as switching to a drug from another class.

Side Effects Of SSRIS

SSRIs can produce adverse effects such as anxiety, nervousness, insomnia, drowsiness, and nausea. Another troublesome side effect is sexual dysfunction (diminished sexual desire, changes in the sensations of arousal, or a compromised ability to achieve orgasm), which occurs in about one third of both men and women taking these drugs. Side effects usually develop within the first

week of starting an SSRI, though they may arise more slowly as blood levels of the medication build up.

Strategies to alleviate sexual dysfunction include choosing a medication with a low rate of sexual side effects (such as bupropion), changing the time you take the medication (possibly to nighttime), reducing the dosage, taking drug holidays (for example, not taking the medication on the weekend), or adding another medication such as the erectile dysfunction drug sildenafil (Viagra).

In addition, many people are troubled by weight gain due to antidepressants.

You should discuss your concerns about the above-mentioned side effects with your doctor.

People Who Should Not Take SSRIS

People taking a combination of drugs that raise serotonin levels can develop a disorder called *serotonin syndrome*. The most common cause is taking an SSRI and a monoamine oxidase (MAO) inhibitor (see page TK) at the same time.

Serotonin syndrome is characterized by altered mental status, neuromuscular abnormalities, and dysfunction of the autonomic nervous system, which controls involuntary reflexes that affect breathing, heart rate, blood pressure, and the digestive tract.

Tricyclic antidepressants (see below) can also contribute to serotonin syndrome.

If you experience troubling symptoms, do not make any changes in your drug regimen on your own—be sure to consult your doctor first.

Tricyclics

Tricyclics—such as amitriptyline (Elavil), desipramine (Norpramin), doxepin (Sinequan), imipramine (Tofranil), nortriptyline (Aventyl, Pamelor), protriptyline (Vivactil), and trimipramine (Surmontil)—are named for their chemical structure: a chain of three rings.

These drugs raise brain concentrations of the neurotransmitters norepinephrine and serotonin by blocking reabsorption of these chemical messengers by the nerve cells that release them.

Tricyclics are used mainly to treat moderate to severe depression; they have proven less effective for chronic low-grade depression (SSRIs work well for this). Each of the tricyclics is believed to be equally effective, but side effects may differ.

Tricyclic therapy is started at a low dose and gradually raised over several weeks.

This slow increase in dosage is less likely to lead to side effects. Moreover, side effects tend to diminish with continued use. For older people, dosages are usually 30–50% lower than the regular adult dosage. When the proper dosage is established, tricyclics can be taken by a patient at bedtime to help bring on sleep rather than cause daytime drowsiness.

Although a positive response to tricyclics could appear within four to six weeks, doctors recommend giving the medication 12 weeks at a full dosage to assess the effects. During this time, blood tests may be ordered to make sure that the drug level is high enough to exert a therapeutic effect but not so high as to be toxic.

Side Effects Of Tricyclics

The most prominent side effects of tricyclics are postural hypotension (dizziness on standing due to a sudden drop in blood pressure), drowsiness, weakness, headache, dry mouth, blurred vision, constipation, nausea, and difficulty urinating.

Many of these side effects can be managed. Drowsiness can be remedied by taking the dose before bedtime (if the doctor approves). Postural hypotension, which can lead to falls and broken bones in older people, can be reduced by standing up slowly after sitting or lying down, and waiting 30 seconds before trying to walk. Pilocarpine (Pilocar) eyedrops may alleviate blurred vision.

Chewing sugar-free gum or candy will help dry mouth. (Be sure to mention dry mouth to your dentist—a lack of saliva can lead to an increase in cavities and oral infections.) Bethanechol (Duvoid, Urabeth, Urecholine) may be prescribed to counteract problems with urination. And constipation can be managed by consuming foods high in fiber and drinking at least eight glasses of water or juice a day.

Amitriptyline (Elavil) and imipramine (Tofranil) are more likely than other tricyclics to cause side effects in older people.

People Who Should Not Take Tricyclics

Tricyclics should not be taken by people with closed-angle glaucoma (a form of glaucoma characterized by a rapid increase in pressure within the eye) and should be used with caution in men who have symptoms of benign prostatic hypertrophy (an enlarged prostate), as they may develop an inability to urinate.

This medical emergency must be treated with catheterization.

The combination of tricyclics with antihistamines can lead to severe constipation, impacted stools, or difficulty urinating, particularly in older adults. In addition, tricyclics (and SSRIs) should not be mixed with the drug selegiline (Eldepryl), a monoamine oxidase inhibitor [see page TK]. Although rare, an interaction between these drugs can cause high fever, tremors, agitation, restlessness, or, in some cases, death.

Tricyclics are not recommended for most people with coronary heart disease because they can cause life-threatening ventricular fibrillation (abnormal rhythm in the heart's lower chambers) in these individuals. Despite the cardiac risks, they are still used to treat depression because they are sometimes the only effective antidepressants for severely depressed older people.

Tetracyclics

The action, efficacy, and side effects of maprotiline (Ludiomil) and mirtazapine (Remeron) are similar to those of the tricyclics. However, maprotiline is more likely to cause seizures than most other antidepressants.

For people who have trouble swallowing pills, a version of mirtazapine that dissolves on the tongue and does not need to be chewed or swallowed whole is available.

People Who Should Not Take Tetracyclics

See the tricyclics section above.

Dopamine Reuptake Inhibitors

Bupropion (Wellbutrin) decreases the reuptake of dopamine, a neurotransmitter and a precursor of other neurotransmitters. This drug causes less drowsiness and fewer side effects than the tricyclics (especially fewer sexual side effects), but on rare occasions it can cause seizures, particularly at higher doses.

Wellbutrin XL is the first drug approved to prevent major depressive episodes in people with seasonal affective disorder (SAD).

Wellbutrin XL has recently become available in generic form, offering great savings. But a word of caution: the active ingredients in the drug are the same, but the inactive ingredients can change the rate at which the medication is absorbed into your blood stream, and can even cause allergic reaction.

Therefore, you need to be alert if you are switching from any name-brand medication to the generic version, and should work with your doctor to see if your dose needs to be adjusted, or you need to be switched back to the name-brand.

Serotonin And Norepinephrine Reuptake Inhibitors

Trazodone (Desyrel) and venlafaxine (Effexor) are serotonin and norepinephrine reuptake inhibitors. Like the tricyclics, these drugs raise brain concentrations of the neurotransmitters serotonin and norepinephrine. They are often the most effective drugs for older people. Possible side effects include nausea, weakness, sweating, insomnia, drowsiness, dry mouth, dizziness, and constipation.

Trazodone is one of the most sedating antidepressants and is actually the most commonly prescribed medication for the treatment of insomnia in the U.S.

Unfortunately, it leaves many people with a morning hangover and next-day grogginess.

People Who Should Not Take Serotonin And Norepinephrine Reuptake Inhibitors

Venlafaxine may increase blood pressure and cholesterol levels in some people, so these need to be monitored in anyone taking this drug.

Monoamine Oxidase (MAO) Inhibitors

MAO inhibitors such as phenelzine (Nardil) and tranylcypromine (Parnate) increase brain levels of norepinephrine, serotonin, and dopamine by blocking the action of the enzyme MAO, which normally inactivates these three neurotransmitters.

MAO inhibitors are effective in many depressed people, especially those whose depression is accompanied by anxiety, panic attacks, heightened appetite, and excessive sleeping.

However, of all the classes of drugs studied in the STAR*D trials, they carried the highest safety risk overall, and the least rate of drug adherence, most likely as a result of the side effects and dietary restrictions they entail.

Side Effects of MAO Inhibitors

MAO inhibitors can cause some of the same side effects as the tricyclics, and these side effects can be reduced in similar ways.

People Who Should Not Take MAO Inhibitors

There are some individuals for whom MAO inhibitors pose greater risks. If you are a heavy drinker, have heart failure or severely impaired liver or kidney function, or take multiple medications for high blood pressure, you should not take an MAO inhibitor.

In addition, MAO inhibitors can cause a sudden, extreme elevation in blood pressure (known as a hypertensive crisis) when people using them take certain drugs or consume foods or beverages containing tyramine. (Tyramine is found in nasal decongestants, cold or allergy medicines, very ripe bananas, beer, and aged or smoked meats, among other things.) People taking an MAO inhibitor must get a complete list of restricted foods and drugs from their doctor.

Normally, the enzyme MAO breaks down any tyramine consumed in the diet, preventing its hypertensive effect. This protective mechanism is disabled by MAO inhibitors, which block the action of MAO in the liver and intestine, allowing tyramine levels to rise and increase blood pressure.

Symptoms of a hypertensive crisis include severe chest pain, excruciating headache, sweating, clammy skin, nausea, and vomiting. Immediate treatment with blood-pressure–lowering drugs is essential. Because of this risk and the

dietary restrictions, MAO inhibitors are now only used as second-line drugs for the treatment of depression, despite their proven efficacy.

A skin patch MAO inhibitor is now available that can be used without dietary restrictions. The patch is sold under the name Emsam, and it delivers the MAO inhibitor selegiline. When selegiline is delivered via a patch at the lowest dose, it does not interfere with the breakdown of tyramine in the digestive tract.

A Word of Warning About "Natural Remedies" For Depression

Despite the availability of a full arsenal of medications proven to be effective for treating depression and anxiety, many people have turned to herbal remedies—which are classified as dietary supplements in the United States and so have not been tested or approved by the U.S. Food and Drug Administration (FDA). No one is sure how well they work as a treatment for depression and anxiety or how they may interact with prescription medications, nor is there any guarantee of the purity of any herbal product you buy.

In addition, one concern with any alternative treatment is that people tend to medicate themselves instead of being evaluated and monitored by a health professional. As a result, they may not recognize worsening symptoms.

St. John's wort, which is extracted from a yellow flowered plant called *Hypericum perforatum*, is the best known of the supplements purported to be natural antidepressants. The American College of Physicians and the American Society of Internal Medicine recently included St. John's wort in their guidelines as a treatment option for mild depression, but two large studies published in the *Journal of the American Medical Association* in 2000 and 2001 found that St. John's wort was no more effective than a placebo for treating major depression.

Thus, the authors recommend that people with major depression not take St. John's wort until well-designed studies support its use. People with mild to moderate depression would be wise to follow the same advice and not take St. John's wort.

Recent reports have illustrated that St. John's wort may not be as benign as it appears. Researchers have shown that St. John's wort lowers blood levels of Crixivan (indinavir), a drug prescribed for HIV (human immunodeficiency virus) infection as well as Sandimmune (cyclosporine), a drug given to prevent organ rejection in transplant patients. Physicians suspect that St. John's wort might interfere with a range of medications, including those prescribed to treat depression, heart disease, seizures, and some cancers. St. John's wort may also cause increased sensitivity to the sun.

Kava, which is prepared from the crushed root of *Piper methysticum* (a shrub-like pepper plant), is marketed as a natural remedy for anxiety and stress. However, the FDA has issued a warning that the supplement can damage the liver. In addition, long-term use of kava may result in allergic reactions, visual

disturbances, or difficulties maintaining. Kava should not be used if you are pregnant, breast feeding, or taking antidepressants.

Given the lack of clinical evidence on herbal supplements generally, and in relation to the medications discussed in this report in particular, herbal supplements for depression are not recommended.

Conclusion:

What Do The STAR*D Results Mean For You?

The STAR*D study results concludes that depression affects different people in different ways, but a wide range of effective antidepressants exist. You should continue to work with your doctor to find the best treatment strategy, to not only reduce symptoms, but achieve remission.

Patience is required. The full effects of a drug may not be experienced for 10 to 12 weeks have passed. You should do your part to adhere to the drug whenever possible, and discuss any side effects you are experiencing with your doctor. You may also have to work with your doctor to adjust doses to find an optimal level, and avoid stopping any medication prematurely.

Further Resources

For more information on Depression and Anxiety, please visit our Depression and Anxiety page at:

http://www.johnshopkinshealthalerts.com/alerts_index/depression_anxiety/16-1.html?st=email&s=SDP_070425_001

The information contained in this Special Report has been derived from *The Johns Hopkins Depression and Anxiety White Paper*

http://www.johnshopkinshealthalerts.com/white_papers/depression_anxiety_wp/digital08_landing.html

and *The Johns Hopkins Depression and Anxiety Bulletin*

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