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## What are the real risks of antidepressants?

*(This article was first printed in the May 2005 issue of the Harvard Mental Health Letter. For more information or to order, please go to <http://www.health.harvard.edu/mental>.)*

Since the late 1980s, America and the world have been enjoying the benefits of the selective serotonin reuptake inhibitors (SSRIs). These **antidepressants** — fluoxetine (Prozac), sertraline (Zoloft), paroxetine (Paxil), fluvoxamine (Luvox), citalopram (Celexa), and escitalopram (Lexapro) — are among the world's most widely prescribed medications. They are remarkably safe and effective. The range of their uses has expanded from depression to anxiety, obsessive-compulsive disorder, eating disorders, and many other psychiatric conditions.

The number of patients who suffer destructive outcomes may be small, but no medical treatment is without risk. In recent years, the side effects of these drugs, from sexual dysfunction to suicidal behavior, have received more attention. Drug makers have been instructed to add warnings about the most serious dangers, particularly the risk of suicide. So the public and professionals are weighing risks and benefits anew. All clinicians and patients should be aware of potential problems, questions, and concerns. We review those issues here and try to put them in perspective.

**Physical symptoms.** Some patients taking SSRIs develop insomnia, [skin rashes](#), headaches, joint and muscle pain, stomach upset, nausea, or diarrhea. These problems are usually temporary or mild or both. A more serious potential problem is reduced blood clotting capacity because of a decreased concentration of the neurotransmitter serotonin in platelets. Patients are at increased risk for stomach or uterine bleeding, and are more likely to require a blood transfusion during or after surgery. This risk is about the same as the risk of bleeding with NSAIDs (aspirin, ibuprofen, naproxen). If patients use SSRIs and NSAIDs at the same time, the risk more than doubles, so they must be combined with care.

**Involuntary movements.** These include tics, muscle spasms, dyskinesia (repetitive muscle movements), parkinsonism (rigid and trembling limbs, a shuffling gait, loss of fine motor control), and akathisia (compulsive restlessness), any of which may be accompanied by severe anxiety. Though rare, these symptoms are more likely in the elderly and in patients taking fluoxetine and citalopram, the SSRIs that remain longest in the body.

Treatments include the anti-anxiety drug diazepam (Valium), the beta-blocker propranolol (Inderal), and antiparkinsonian drugs such as bupropion (Wellbutrin). It may also help to switch to a different kind of antidepressant.

**Sexual effects.** For many patients, SSRIs diminish sexual interest, desire, performance, satisfaction, or all four. In men, SSRIs can delay or inhibit [ejaculation](#), and in women, delay or prevent orgasm. They may also hinder lubrication of the vagina, erection of the penis, and engorgement of the clitoris. And many users of SSRIs who can function physically lose interest in sex.

Lowering the dose may help, although the patient may lose the drug's benefit. Another solution is adding or substituting bupropion (Wellbutrin), which works by a different mechanism and does not generally cause sexual side effects.

Sildenafil (Viagra) or tadalafil (Cialis), taken an hour before sex, helps maintain an erection in men by increasing blood flow to the penis. The main potential side effects are headaches, flushing, upset stomach, and heartburn. Used by a person taking nitrates for angina, these drugs could cause a dangerous fall in blood pressure. They have not clearly shown benefits for women in controlled trials.

**Drug interactions.** SSRIs are broken down in the liver by a group of enzymes known as the cytochrome P450 system. By engaging these enzymes, SSRIs may bump out another drug that requires the same breakdown process, thus increasing its blood level and prolonging its action. The danger is greatest with fluoxetine and paroxetine. Physicians who prescribe SSRIs must know about other drugs a patient is taking so that the dose can be adjusted.

If an SSRI is taken along with another drug that enhances serotonin activity, a rare condition called the serotonin syndrome may develop — racing heart, sweating, high fever, high blood pressure, and sometimes delirium. In particular, SSRIs should not be mixed with certain other medications, especially the herbal remedy St. John's wort, monoamine oxidase inhibitors such as phenelzine (Nardil), and clomipramine (Anafranil). The serotonin syndrome has also been reported when an SSRI is combined with lithium, the standard treatment for bipolar disorder.

**The elderly.** SSRIs are safer than tricyclic antidepressants for older people because they do not disturb heart rhythms and rarely cause dizziness that results in falls. But liver function is less efficient in older people, so there is a greater risk of drug interactions involving the cytochrome P450 system. For that reason, older people do best with rapidly metabolized drugs like sertraline.

**Loss of effectiveness.** Any antidepressant may lose its effect after months or years, sometimes because the brain has become less responsive to the drug (tolerance). Solutions include increasing the dose and

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switching to another antidepressant with a different mechanism of action.

**Discontinuation symptoms.** Symptoms that may occur on stopping an SSRI include dizziness, loss of coordination, fatigue, tingling, burning, blurred vision, insomnia, and vivid dreams. Less often, there may be nausea or diarrhea, flu-like symptoms, irritability, anxiety, and crying spells. "Discontinuation syndrome" is a better description than "withdrawal reaction," a phrase associated with addiction. The syndrome is usually (but not always) mild and brief, peaking in the first week and quickly fading.

Although none of these drugs should be stopped abruptly, paroxetine tends to produce the most intense discontinuation symptoms. Here is a place where the longer-lasting drugs have an advantage; some clinicians switch to fluoxetine before gradually lowering the dose.

**Antidepressants before birth.** Some (but not all) studies have found a higher than average risk for low birth weight and premature delivery when antidepressants are taken during pregnancy, especially in the last three months. At birth, infants may suffer withdrawal symptoms, including jitters, crying, irritability, shivering, and, rarely, seizures. One study, correcting statistically for other factors including the mother's depression, found more respiratory distress in infants exposed to paroxetine in the last months of pregnancy. The symptoms were most intense in the first few days and usually disappeared within a month.

Reports of discontinuation symptoms are difficult to interpret because they do not come from controlled experiments. Risks to the fetus must be weighed against the considerable risks of depression to both mother and child. More seriously depressed women are more likely to need antidepressant drugs while pregnant, and depression itself can affect the unborn child. In such situations, it may be essential to prescribe antidepressants for pregnant women.

**Breast-feeding.** Similar cautions apply to nursing mothers. A meta-analysis published in 2004 indicated that the quickly eliminated drugs paroxetine and sertraline do not reach significant levels in breast milk, but fluoxetine and citalopram do.

**Suicide.** The risk that antidepressants will incite violent or self-destructive actions is the subject of renewed controversy. Suicidal thoughts (although no suicides) in patients taking SSRIs were first reported in 1990, shortly after the drugs were introduced. An FDA committee rejected the association, and most mental health professionals accepted that conclusion. But the issue was never completely settled.

One reason for concern is the increasing number of children and adolescents receiving prescriptions for antidepressants. An analysis of clinical trials in patients under age 18 found that SSRIs raised the risk of suicidal thinking when compared with a placebo. Many studies have followed, and although results vary, there is a consistent trend. When compared with a placebo, all antidepressants, including SSRIs, seem to double the risk of suicidal thinking, from 1%–2% to 2%–4%, in both children and adults.

In October 2004, after much hesitation and pressure from parents and Congress, the FDA issued a Black Box Warning for physicians and pharmacists — its strongest available measure short of withdrawing a drug from the market. The warning is placed on package inserts for all antidepressants in common use. It mentions the risk of suicidal thoughts, hostility, and agitation in both children and adults, specifically citing statistical analyses of clinical trials. The FDA has also issued a public advisory to parents, physicians, and pharmacists, and it will develop an information guide to be distributed with each new prescription.

Professional organizations are also acting. The American Academy of Child and Adolescent Psychiatry has established a committee to monitor controlled trials, set standards, and promulgate guidelines for the use of drugs in children. The Academy will also work with the National Institute of Mental Health (NIMH) to publish a review of these issues and a guide for investigators. The American Medical Association is preparing an independent review of the evidence on risks and benefits of antidepressants.

Self-destructive feelings and thoughts in patients taking SSRIs may be the result of anxiety or akathisia. Sometimes a person with hidden bipolar disorder receives an antidepressant and develops an irritable manic reaction. Some patients may recover their energy and therefore their ability to act before mood improves or hope returns. The danger is greatest in the first few weeks of treatment. If a patient begins to have suicidal thoughts after many months on an antidepressant, the drug is probably not to blame. It's more likely to be caused by the underlying illness.

A bad outcome can be avoided by regular follow-up and close monitoring. Patients should be warned that there is a slight chance they will feel worse for a while, and they should let their prescribing clinicians know immediately if they begin to feel worse or develop new symptoms, especially after changing the medication or the dose.

**Weighing the risks for children.** Those who think antidepressants and other psychiatric drugs are being prescribed too freely for children and adolescents may feel vindicated by these developments. They doubt that we know enough about the long-term effects of antidepressants and other drugs on children's growth or developing brains.

As of early 2005, only fluoxetine is FDA-approved for major depression in patients under age 18. Fluoxetine, fluvoxamine, and sertraline are approved for childhood obsessive-compulsive disorder. In a clinical trial, paroxetine was found effective for social anxiety disorder in children. But the difference between drug and placebo is moderate, and psychotherapy is generally equally effective. The NIMH is also sponsoring a study of antidepressants and psychotherapy in adolescents who have attempted suicide.

The warnings and regulations have influenced professional judgments. The number of antidepressant prescriptions for children, which rose rapidly throughout the 1990s, has begun to fall almost as precipitously. According to a company that processes prescriptions for HMOs and employers, child and adolescent antidepressant use dropped 16% in the last three months of 2004.

Overall, pediatricians and general practitioners write about a third of antidepressant prescriptions for children and adolescents. It's expected that many of them will stop prescribing these drugs and instead refer patients with suspected depression to mental health professionals. One optimistic view is that this change will result in closer monitoring. And in the future SSRIs may be prescribed mostly for children and adolescents with persistent or severe symptoms that are not responding to psychotherapy.

**The other side.** The practical significance of the findings on suicidal thinking is still uncertain. The lifetime

suicide rate of people with major depression is 15%, and depression can also be lethal in other ways; for example, a history of major depression doubles the risk of heart disease. And it has been estimated that only 25% of cases of major depression receive adequate treatment of any kind, either drugs or psychotherapy. The adolescent suicide rate declined nearly 15% in the United States between 1985 and 1999, while use of SSRIs in that age group was rising by nearly 70%. Only 20% of adolescents who commit suicide have ever taken an antidepressant drug. Ironically, the most worrisome potential side effects of SSRIs — loss of libido and suicidal thinking — are also common symptoms of depression. Another irony is that SSRIs have largely replaced the older tricyclic antidepressants partly because they cannot be used to commit suicide.

Some will always think that drugs are overused, others that they are not used enough. Decisions about SSRIs engage professional loyalties — psychologists naturally tend to be more skeptical about drugs than psychiatrists — as well as economic interests, including concern about the rising costs of health care. There are larger issues, too — whether the current popularity of drug treatment means that psychotherapy is being neglected and depression understood too exclusively as a biochemical problem.

Research in genetics, pharmacology, and neuroscience may eventually reduce uncertainty and anxiety by helping us choose which antidepressant will have the greatest benefits with the fewest side effects for a given patient. Meanwhile, the period of adjustment we have been going through in the early 2000s should help bring judgments on the risks and benefits of antidepressants into better balance.

**Resources**

Information on antidepressant research findings, guidelines, and regulations is available on the Web.  
U.S. Food and Drug Administration  
[www.fda.gov/cder/drug/antidepressants/default.htm](http://www.fda.gov/cder/drug/antidepressants/default.htm)  
National Institute of Mental Health  
[www.nimh.nih.gov/healthinformation/antidepressant\\_child.cfm](http://www.nimh.nih.gov/healthinformation/antidepressant_child.cfm)  
American Academy of Child and Adolescent Psychiatry  
[www.aacap.org/announcements/psychiatricmeds.htm](http://www.aacap.org/announcements/psychiatricmeds.htm)

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For more references, please see [www.health.harvard.edu/mentalextra](http://www.health.harvard.edu/mentalextra).

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