

Weighing the Benefits and Risks of SSRI Antidepressants for Youth

Parents, physicians and the public attempting to make sense of the controversy about antidepressants are torn between unproven claims and counter-claims about the drugs' benefits and risks. People cannot make an informed treatment decision unless they know the demonstrated risks and benefits. Following the FDA-mandated black box warnings (October 2004) of a twofold increased risk of suicidality in children—4% in those on an antidepressant compared to 2% in those on placebo—there was a dramatic 20% to 25% drop in SSRI prescriptions for children under 18. Robert Epstein, M.D., chief medical officer of Medco Health, which had analyzed the data, expressed confidence:

"[the data] appears to support [the idea] that **information and education is a powerful tool to improve our health care delivery system.**"

<http://pn.psychiatryonline.org/cgi/content/full/39/20/9>

In this spirit of supporting informed decisions, we summarize the demonstrated benefits and risks of newer antidepressants (also referred to as SSRIs/SNRIs). Our tabular summary was prompted in part by a new report issued by the American College of Neuropsychopharmacology (ACNP) Task Force, "SSRIs and Suicidal Behavior in Youth," (January 2006). <http://pn.psychiatryonline.org/cgi/content/full/41/1/29?etoc>

The ACNP report acknowledges that "SSRIs and other new-generation antidepressant drugs, in aggregate, are associated with a small increase in the risk of suicidal thinking or suicide attempts in youth." This conclusion emerged from an FDA-sponsored analysis by researchers at Columbia University of the clinical trials of antidepressants in adolescents and children available to the FDA, and which the manufacturers and the FDA put in a black box warning for all antidepressants. The ACNP report is useful in summarizing the benefits derived from the same studies, and we have included the ACNP efficacy measure in our table.

An informed treatment decision must consider all of the demonstrated risks and benefits. Unfortunately, neither of the meta-analyses conducted by FDA/Columbia or the ACNP included risks of adverse effects besides suicidality. Nevertheless, information about these adverse effects emerged in clinical trials, and that information is described in the product labels for each drug. Using a common assumption that underlies the ACNP analysis of benefits and the FDA/Columbia analysis of risks—namely, that antidepressants are similar in their clinical effects—we summarize the adverse events listed in the tables of the three most popular drugs (Paxil, Prozac and Zoloft).

Specifically, we show the adverse events that are listed for any of these drugs in tables of adverse events (contained in the drugs' label) for which the risk was greater for patients receiving the drug than for patients receiving placebo. That is, the table shows the excess risk (%) of the drug over and above the

background risk that occurred with placebo.

Our table summarizes the benefits and risks that were demonstrated in randomized controlled clinical trials of these drugs—the most reliable form of clinical evidence. See: <http://ahrp.org/risks/SSRIrbTable.html> Events that occur at a frequency too rare to be seen in the trials, or events that occur in types of people not included in the trials (e.g., pregnant women), are not included. This summary cannot provide a comprehensive listing of adverse effects, and is not intended as a substitute for reading all of the information in the product label. We urge those interested in these drugs to read the labels carefully.

The tables presented in drug labels have limitations. Drug labels are not standardized, and different manufacturers describe different adverse events or use different terms to describe the same events. For instance, two manufacturers display adverse events that occurred in greater than 2% of treated patients, while another manufacturer showed adverse events that occurred in greater than 1% of treated patients. In addition, manufacturers do not consistently tabulate results from pediatric trials in the same way they do for adult trials.

<http://www.fda.gov/cder/drug/infopage/fluoxetine/default.htm>;

<http://www.fda.gov/cder/drug/infopage/sertraline/default.htm>;

<http://www.fda.gov/cder/drug/infopage/paroxetine/default.htm>

Nevertheless, and as described in the Prozac label, “The overall profile of adverse events [in pediatric trials] was generally similar to that seen in adult studies.” Of course, there could be additional adverse events that occur in children. Furthermore, the clinical trials often exclude patients who might be at increased risk of adverse effects. Information in labels may combine trials of different durations, and the precise risk period may be unclear. However, most trials are brief in duration (weeks rather than years) and cannot address the effects of long-term use.

More generally, and as described in all the labels, “the figures in the tables cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials.” Nevertheless, the figures are offered by the FDA and manufacturers because they “do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side effect incidence rate in the population studied.”

<http://ahrp.org/risks/label/Prozac.pdf>;

<http://ahrp.org/risks/label/Paxil.pdf>

<http://ahrp.org/risks/label/Zoloft.pdf>

BENEFITS

One compelling rationale frequently offered in support of using antidepressants is that depression is an important public health problem that carries a risk of suicide. Indeed, depression can be a serious, even fatal, condition. **But antidepressants have never been demonstrated to prevent suicide.** It follows that prevention of suicide, a goal everyone shares, is not supported by reliable scientific evidence as a reason to take antidepressants. In fact, manufacturers of antidepressants cannot make any claim about the drugs preventing suicide, but they must include in the label a precaution informing adults and children that antidepressants may lead to clinical worsening and increase the risk of suicide compared with placebo.

People may be surprised to learn that drug manufacturers are not required to state in the label how well (or poorly) a drug works—or how often it failed to demonstrate a benefit greater than placebo in clinical trials. Furthermore, the standard used by drug companies and the FDA to measure effectiveness of antidepressants in depression is not improved survival or even improvement of meaningful life functions (e.g., self care, eating, sleeping, school work, social interactions, developing friendships, etc.). Instead, an antidepressant drug's benefit is measured by how people respond to an interview graded on a depression scale such as the Hamilton Depression (HAM-D) Rating Scale which comprises 21 multiple choice responses. In pediatric trials, a similar questionnaire, the Children's Depression Rating Scale (CDRS-R), is often used. For these questionnaires to be valid, patients must accurately recall their thinking and behavior and report it truthfully.

ACNP estimates that the “number needed to treat” (NNT) in order to elicit one positive response on a depression questionnaire is 17.4 children. That is, for every 17 children treated with an SSRI, one child will respond positively on a questionnaire. In other words, for the indication of depression, **“effective” means a one in 17 or 6% chance of improvement as rated in a questionnaire score.**

Antidepressants in the class, Selective Serotonin Reuptake Inhibitors, are nonspecific in their effects and are approved for many other indications besides major depressive disorder, including:

- Anxiety
- Obsessive-compulsive disorder
- Post-traumatic stress disorder
- Panic disorder
- Premenstrual dysphoric disorder
- Social anxiety disorder
- Generalized anxiety disorder
- Bulimia nervosa

(For most of these indications, efficacy was measured using different questionnaires. Further details can be obtained from product labels.)

RISKS

Risks are challenging to identify and even more difficult to quantify because drug companies design short-term clinical trials to demonstrate efficacy, not to detect adverse effects. That is the main reason that it took so long for the FDA to develop the black box warning for suicidality. It was not until the FDA combined studies from many antidepressants in a meta-analysis that the risk of suicidal behavior, identified by Dr. Teicher (1990) more than a decade ago, became statistically significant and included as a black box warning.

Manufacturers' labels for Prozac, Zoloft and Paxil show that the 2% excess risk of suicidality is not the only worrisome adverse event reported during pediatric and adult clinical trials. Nor is an increased risk of suicide the only symptom of depression also associated paradoxically with antidepressants. Every antidepressant label describes a major depressive episode as including at least 4 of the following symptoms:

- change in appetite
- change in sleep
- psychomotor agitation or retardation
- loss of interest in usual activities or decreased sexual drive
- fatigue
- feelings of guilt or worthlessness
- slowed thinking or impaired concentration
- suicide attempt or suicidal ideation

Adverse events that occur at more than double the frequency on antidepressants than on placebo include many of these same symptoms:

- decreased appetite, weight loss
- somnolence, insomnia
- agitation
- decreased libido, sexual dysfunction, anorgasmia
- fatigue, asthenia
- confusion, abnormal thinking
- anxiety, nervousness, akathisia
- suicidality

The following ADDITIONAL risks are enumerated in the FDA Patient Information Sheet (7-20-2005) (<http://www.fda.gov/cder/drug/InfoSheets/patient/fluoxetinePIS.htm>)

“Taking antidepressants may increase suicidal thoughts and actions in about 1 out of 50 people 18 years or younger.”

“FDA is highlighting that adults being treated with antidepressant medication, particularly those being treated for depression, should be watched closely for worsening of depression and for increased suicidal thinking or behavior.”

What Are The Risks?

Suicidal thoughts or actions: See FDA Alert.

Rash and possible allergic reactions: Antidepressants may cause serious skin, lung and allergic-type reactions. Contact your healthcare professional right away if you get a skin rash or hives, have problems breathing, or get swelling of your tongue, lips, or throat.

Bleeding problems: Antidepressants may cause bleeding problems, especially if taken with aspirin, NSAIDs (nonsteroidal anti-inflammatory drugs, such as ibuprofen or naproxen), or other drugs that affect bleeding.

Mania: You may become hyperactive, excitable or elated.

Seizures: You may experience a seizure (convulsion), even if you are not taking fluoxetine close in time with a MAOI.

Weight loss: Antidepressants can cause weight loss. Children who take it for a long time should have their growth and body weight measured regularly.

Pregnancy: Tell your healthcare professional if you are or may be pregnant because babies delivered to mothers taking antidepressants late in pregnancy have developed problems, such as difficulty breathing and feeding.

Sexual problems: You may have problems with impotence (erectile dysfunction), abnormal ejaculation, difficulty reaching orgasm, or decreased libido (sexual desire).

Other side effects include nausea, difficulty sleeping, anxiety, nervousness, and sleepiness.

Tell your healthcare professional about all your medical conditions, especially if you have liver or heart disease, or diabetes. Tell your healthcare professional if you are breast-feeding or plan to breast-feed your baby.

It was not uncommon for people in clinical trials (e.g., >10%) to stop taking antidepressants because they experienced adverse events. Whether or not one experiences a side effect, however, it is important to recognize that stopping antidepressant medication entails special risks, and it is not advisable to abruptly discontinue taking antidepressants. As described in the FDA Patient Information Sheet:

Stopping medication: Do not stop taking an antidepressant suddenly because you could get side effects. Your healthcare professional will slowly decrease your dose.