SSRIs: Are They As Safe As Promised? Part 1

by Gary Null, PhD and Martin Feldman, MD

Sixteen years have passed since Prozac, the antidepressant drug, was introduced to the US market and quickly achieved the label of a "wonder drug." During that time, Prozac has indeed helped many people who suffer from severe depression. But the early claims that Prozac would alleviate depression without causing harmful side effects have not been realized.

In fact, just the opposite has proved to be true. Prozac has produced serious side effects in some users, prompting a host of lawsuits against Eli Lilly & Co., the drug's manufacturer. These adverse effects include akathisia (a condition in which a person feels compelled to move about), permanent neurological damage, and suicidal obsession and acts of violence.

Despite the emergence of these reactions, Prozac has gone on to generate more than $21 billion in sales for Eli Lilly,[1] to be taken by more than 40 million people worldwide,[2] and to lead a new class of medication – the selective serotonin reuptake inhibitors (SSRIs). In addition to fluoxetine (Prozac), the SSRIs include paroxetine (Paxil), sertraline (Zoloft), fluvoxamine (Luvox), and citalopram (Celexa).

This two-part article focuses on serious side effects associated with SSRIs, particularly Prozac. (Our report does not include the newest entrant to this class – escitalopram oxalate (Lexapro) – which was launched by Forest Laboratories, the manufacturer of Celexa, in late 2002. This new drug consists of the single active isomer of Celexa.)[3] The most controversial issue surrounding the use of SSRIs – a possible connection to suicidal thoughts and behavior in some users – made news in mid-2003 when the Food and Drug Administration recommended that Paxil not be used to treat depressed children and adolescents because regulators were reviewing reports from clinical trials of an increased risk of suicidal thinking and suicide attempts in young users of the drug.[4]

Zoloft, Paxil, and Prozac were the top-selling antidepressants in the US in 2001, and antidepressants themselves were the largest category of prescription drug that year, with US retail sales of $12.5 billion.[5] Prozac was the leading antidepressant worldwide in 2000, but its share of prescriptions has been declining since the mid-1990s due to competition from other drugs and from generic fluoxetine.[6] Eli Lilly's US sales of fluoxetine products fell 73% in 2002 following the introduction of generic fluoxetine here in August 2001.[7] Generic paroxetine and fluvoxamine also are available in the US market.

Although the Prozac era has ended for Eli Lilly, the availability of less costly generics means that fluoxetine may be more affordable for tens of millions of uninsured people.[8] And in addition to gaining approval for Prozac for indications besides depression (obsessive-compulsive disorder, bulimia nervosa, and panic disorder), Eli Lilly now markets two Prozac-related products that have their own patents: Sarafem is the version of Prozac approved in 2000 for the treatment of premenstrual dysphoric disorder (PMDD). It was the first prescription drug in the US with this indication. The second drug is Prozac Weekly, intended for the longer-term treatment of depression when symptoms have stabilized. It was approved in 2001.[9-11]

IMS Health has noted a trend toward "lifestyle indications" for anti-depressants.[12] In addition to major depression and OCD, both Paxil and Zoloft are indicated for panic disorder, posttraumatic stress disorder, and social anxiety disorder. Zoloft also is approved for premenstrual dysphoric disorder, while Paxil also is approved for generalized anxiety disorder.[13,14] Doctors, for their part, prescribe SSRIs for a wide range of conditions, such as headaches, substance abuse, eating disorders, back pain, impulsivity, upset stomach, irritability, hair pulling, nail biting, premature ejaculation, sexual addictions, and attention deficit disorder.[15]

One growing market for SSRIs is their use with children, even though some studies have found that antidepressants are no more effective than placebos in these patients.[16-22] A study in the *Journal of the American Medical Association* in 2000 found that psychotropic medications prescribed to preschoolers had "increased dramatically between 1991 and 1995" in the three sites studied.[23] An analysis of prescription claims among young Medicaid patients in North Carolina found that the use of Ritalin-type stimulants and Prozac-type antidepressants among children rose dramatically in the 1990s and that more were taking both drugs at once. In 1998, 10.7% of children aged 6 to 14 were receiving stimulants and 1.7% were receiving SSRIs (30% of these also took stimulants). Lead author Jerry Rushton, MD, MPH, stated, "...the consistent increase in SSRI use and in dual prescriptions is especially surprising. We need further information about whether this is due to new unrecognized mental disorders, substitution for other therapies, or overprescription."[24]

Serotonin and side effects

Prozac relieves depression by affecting the level of serotonin, a neurotransmitter that connects receptor sites and fires nerve cells. Joseph Glenmullen, MD, a clinical instructor in psychiatry at Harvard Medical School, explains in his book *Prozac Backlash* that the drug inhibits the reuptake of serotonin – a process in which a cell that releases this chemical messenger reabsorbs any unused portion of it. By blocking the reuptake of this neurotransmitter, Prozac boosts the level of serotonin and prolongs the serotonin signals in the brain.[25]

Dr. Glenmullen points out, however, that neurotransmitters like serotonin, adrenaline, and dopamine are connected by complex circuitry and function interdependently. Changes in one neurotransmitter can set off changes in another. Thus, the idea that Prozac-type drugs work "selectively" on serotonin is an illusion. When the level of serotonin is artificially increased, the primary reaction in the brain is a drop in dopamine – a powerful secondary effect that was not understood when the new class of serotonin boosters was introduced. The severe effects of the SSRIs are thought to be caused by the connections between the serotonin and dopamine systems. "Drugs producing a dopamine drop are well known to cause the dangerous side effects that are now appearing with Prozac and the other drugs in its class," Dr. Glenmullen writes. His term for these compensatory reactions in the brain is "Prozac backlash."[26]

Peter R. Breggin, MD, also reports in *Talking Back to Prozac: What Doctors Aren't Telling You About Today's Most Controversial Drug*, that Prozac acts as a stimulant to the nervous system.[27]

Therefore, it can produce side effects that mimic those of amphetamines and are exaggerations of the desired effects of Prozac in relieving depression.

According to Dr. Breggin, the FDA psychiatrist who wrote the agency's safety review of Prozac stated that the drug's effects – including nausea, insomnia, and nervousness – resembled the profile of a stimulant drug rather than a sedative.[28] Dr. Breggin notes that nearly all of the Prozac side effects listed in the *Physician's Desk Reference* "fit into the stimulant profile." Among others, these stimulant symptoms include headaches, nervousness, insomnia, anxiety, agitation, tremors, weight loss, nausea, diarrhea, mouth dryness, anorexia, and excessive sweating.[29] He adds in *The Antidepressant Fact Book* that all of the SSRIs can cause insomnia, anxiety, agitation, and nervousness. These same effects and others are caused by the classic stimulants – methylphenidate, amphetamine, methamphetamine, Ecstasy, and cocaine.[30]

A drug that acts as a stimulant also can overstimulate the body systems. In *Talking Back to Prozac,* Dr. Breggin offers the example of a person who takes Prozac to relieve depression (the beneficial effect) and suffers from agitation and insomnia (the negative effects). These adverse reactions "are inherent in the stimulant effect that produces feelings of energy and well-being," he writes. "In this sense, the difference between 'therapeutic effects' and 'toxic effects' are merely steps along a continuum from mild to extreme toxicity."[31]

The Food and Drug Administration has received approximately 45,000 adverse reaction reports on Prozac.[32] It is not unusual for serious adverse effects to surface after a drug has hit the market, perhaps requiring that a major new warning be added to the label or that the drug be withdrawn. The FDA informs doctors, but not the public, that the approval of a drug does not mean it is safe.

An analysis of 548 new drugs approved between 1975 and 1999 was published in the *Journal of the American Medical Association* in 2002. It found that 56 of the drugs acquired a black box warning or were withdrawn (16 drugs) from the market. There was a 20% chance that problems will arise with any given drug after its approval. The researchers conclude that serious adverse drug reactions commonly emerge after FDA approval. They add, "The safety of new agents cannot be known with certainty until a drug has been on the market for many years."[33,34]

Dr. Glenmullen says that popular psychiatric drugs follow a "10-20-30 year pattern" in revealing their dangerous effects and falling into disfavor: About 10 years after their debut, the earliest signs of problems appear. At 20 years, there is enough data for the problems to be undeniable and a significant number of physicians to voice their concerns. At 30 years (or more), professional organizations and regulators actively work to stop overprescribing of the drug. At this point, drugs have become passé and lost their patent protection, and the manufacturers move on to more profitable drugs "that can be promoted as 'safer' because their hazards are not yet known."[35]

Comparisons of efficacy

The SSRIs have no more specific effect on depression than do other antidepressants, including the tricyclics and monoamine-oxidase inhibitors (MAOIs), according to Charles Medawar. As he explains in "The Antidepressant Web," patients generally respond to antidepressants in about 60% to 70% of cases, while the typical response to placebo is 30% to 35%. Therefore, the popularity of SSRIs is due to the fact that most experts believe they are safer or otherwise more acceptable than the alternatives. And, in fact, promotional messages for SSRIs state three advantages: the drugs produce fewer unwanted side effects, are more acceptable to more patients, and are safer in overdose.[36]

Despite the safety-related claims made in the medical literature, however, "the evidence overall does not suggest that SSRIs show any great and decisive safety advantage over alternatives in day to day use," says Medawar. Consider the results of trials comparing SSRI efficacy and safety with that of other antidepressants: "Two independent meta-analyses, each starting with a careful search of the literature to identify all properly controlled trials, have reached broadly similar conclusions – the SSRIs do have the edge on alternatives, but not by much."[37] One analysis of 62 trials found a 49% dropout rate for SSRIs versus a 54% rate for tricyclic

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antidepressants.[38] A second analysis of 63 trials (16 comparing an SSRI with a non-tricyclic) found that 3% fewer people stopped taking an SSRI because of the side effects.[39]

Other recent reviews also have found that the newer antidepressants are no more or less effective in treating depression than older-generation drugs.[40,41] In a government study conducted by Dr. Cynthia Mulrow and colleagues, the researchers analyzed more than 300 randomized controlled trials and concluded there were no significant differences in efficacy between newer and older agents or in overall discontinuation rates. Fewer people taking SSRIs stopped treatment due to adverse effects than those taking first-generation tricyclics (the rate difference was 4%). More than 80 studies did find that newer antidepressants were more effective than placebo in treating major depression in adults. The response rate was 50% for the drugs, versus 32% for placebo.[42,44]

A more troubling conclusion was reached by Dr. Irving Kirsch and colleagues who analyzed data sent to the FDA for approval of the six most commonly prescribed antidepressants between 1987 and 1999 (Prozac, Paxil, Zoloft, Effexor, Serzone, and Celexa).[45] Their analysis found that the response to placebo was almost as great as the response to the antidepressants. The mean difference on the Hamilton Rating Scale for Depression was two points, according to a report in *Psychiatric Times*. The difference was statistically, but not clinically, significant.[46] The article states, "More than half of the clinical trials sponsored by the pharmaceutical companies failed to find significant drug/placebo difference, and there were no advantages to higher doses of antidepressants." The authors add, "The small difference between antidepressant and placebo has been referred to as a 'dirty little secret' by clinical trial researchers..."[47]

Several recent studies have reported similar results, finding that an SSRI did not differ significantly from placebo in the treatment of depression.[48-50]

Part 2: Serious adverse reactions that have been associated with Prozac and other SSRIs.

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