Selective serotonin reuptake inhibitors (SSRIs)

Selective serotonin reuptake inhibitors (**SSRIs**) are a class of antidepressants for treating depression, anxiety disorders and some personality disorders. Studies found that SSRIs, as a side effect of their action, may cause in many people a delay of sexual climax, so they can be used to develop drugs specifically targeted to treat premature ejaculation.

SSRI drugs are designed to allow the available neurotransmitter serotonin to be utilized more efficiently. A low level of utilization of serotonin is currently seen as one among several neurochemical symptoms of depression. Low levels of serotonin in turn can be caused by an anxiety disorder, because serotonin is needed to metabolize stress hormones

These medications evolve their effects at the serotonin transporter. They increase the extracellular level of the neurotransmitter serotonin by inhibiting its reuptake into the presynaptic cell. They have no or only weak effects on other monoamine transporters, thus having little direct influence on the level of other neurotransmitters. That distinguishes them from the older tricyclic antidepressants (TCAs), thus they are named *selective*. SSRIs are considered to be considerably safer than TCAs, since the toxic dose is much higher and they are said to have fewer and weaker side effects and drug interactions.

- citalopram (*Celexa, Cipramil, Emocal, Sepram*)
- escitalopram oxalate (*Lexapro, Cipralex, Esertia*)
- fluoxetine (*Prozac, Fontex, Seromex, Seronil, Sarafem, Fluctin (EUR)*)
- fluvoxamine maleate (*Luvox, Faverin*)
- paroxetine (*Paxil, Seroxat, Aropax, Deroxat*)
- sertraline (*Zoloft, Lustral, Serlain*)
- dapoxetine (no known trade name)

Medical indications

The main indication for SSRIs is *major depression*. Apart from this, SSRIs are frequently prescribed for *anxiety disorders*, *panic disorders*, *obsessive-compulsive disorder (OCD)*, social phobia and *eating disorders*. Though not specifically indicated by the manufacturers, they are also sometimes prescribed to treat *irritable bowel syndrome (IBS)*. Additionally, SSRIs have been found to be effective in treating *premature ejaculation* in up to 60% of men.

Contraindications / drug interaction

SSRIs are contraindicated with concomitant use of MAOIs (monoamine oxidase inhibitors). This can lead to increase serotonin levels which could cause a serotonin syndrome. People taking SSRIs should also avoid taking pimozide (a diphenylbutylpiperidine derivative). The non-opioid analgesic tramadol hydrochloride (or Ultram, Ultracet) can, in rare cases, produce seizures when taken in conjunction with an SSRI or tricyclic antidepressant.

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Mode of action

Basic understanding

In the brain, messages are passed between two nerve cells via a synapse, a small gap between the cells. The cell that sends the information releases neurotransmitters (of which serotonin is one) into that gap. The neurotransmitters are then recognized by receptors on the surface of the recipient (*postsynaptic*) cell, which upon this stimulation, in turn, relays the signal. About 10% of the neurotransmitters are lost in this process, the other 90% are released from the receptors and taken up again by monoamine transporters into the sending (*presynaptic*) cell (a process called *reuptake*).

Some theories link depression to a lack of stimulation of the recipient neuron at a synapse. To stimulate the recipient cell, SSRIs inhibit the reuptake of serotonin. As a result, the serotonin stays in the synaptic gap longer than it normally would, and has the chance to be recognized again (and again) by the receptors of the recipient cell, which can finally be stimulated fully. Why the overall level of stimulation by serotonin exceeds the significance of the signalling pattern is not addressed by such theories. The assertion they make is that if someone cannot hear you, the solution is to add an echo and a slow fade. Conventional signals theory, as applied to neuronal signal propagation, says that this would reduce the useful bandwidth, efficiency, the amount of information that can be carried, and blur out the signal. Since nerves carry so much more information from place to place than depression level, and "stimulated fully" is so close to "saturated and no longer passing a fluctuating signal", the "receptor can finally be stimulated fully" theory is notable for not posing these critical questions, much less attempting to provide answers to them.

Pharmacodynamics

SSRIs inhibit the reuptake of the neurotransmitter serotonin (*5-hydroxytryptamine* or *5-HT*) into the presynaptic cell, increasing levels of 5-HT within the synaptic cleft.

But there is one counteracting effect: high serotonin levels will not only activate the postsynaptic receptors, but also flood presynaptic autoreceptors, that serve as a feedback sensor for the cell. Activation

of the autoreceptors (by agonists like serotonin) triggers a throttling of serotonin production. The resulting serotonin deficiency persists for some time, as the transporter inhibition occurs downstream to the cause of the deficiency, and is therefore not able to counterbalance it. The body adapts gradually to this situation by lowering (downregulating) the sensitivity of the autoreceptors.

Of greater importance is another adaptive process: the downregulation of postsynaptic serotonin 5-HT_{2A} receptors.

These (slowly proceeding) neurophysiological adaptions of the brain tissue are the reason why usually several weeks of continuous SSRI use are necessary for the antidepressant effect to become fully manifested.

Interaction with carbohydrate metabolism

Serotonin is also involved in regulation of carbohydrate metabolism. Few analyses of the role of SSRI's in treating depression cover the effects on carbohydrate metabolism from intervening in serotonin handling by the body.

Neuroprotection

Studies have suggested that SSRIs may promote the growth of new neural pathways.[1] Also, SSRIs may protect against neurotoxicity caused by other compounds (for instance MDMA and Fenfluramine) as well as from depression itself.

SSRIs versus TCAs

SSRIs are described as 'selective' because they affect only the reuptake pumps responsible for serotonin, as opposed to earlier antidepressants, which affect other monoamine neurotransmitters as well. Because of this, SSRIs lack some of the side effects of the more general drugs.

There appears to be no significant difference in effectiveness between SSRIs and tricyclic antidepressants, which were the most commonly used class of antidepressants before the development of SSRIs.[2] However, SSRIs have the important advantage that their toxic dose is high, and, therefore, they are much more difficult to use as a means to commit suicide. Further, they were initially claimed to have fewer and milder side effects.

SSRIs versus 5-HT-Prodrugs

Serotonin cannot be administered directly because when ingested orally, it will not cross the blood-brain barrier, and therefore won't have an effect on brain functions. Also, serotonin would activate *every* synapse it reaches, whereas SSRIs only *enhance a signal* that is already present, but too weak to come through.

Biosynthetically serotonin is made from tryptophan, an amino acid. If depression is caused by lack of serotonin, rather than insensitivity to it, SSRIs alone will not work well, whereas supplementing with

tryptophan will. In 1989, the Food and Drug Administration made tryptophan available by prescription only, in response to an outbreak of eosinophilia-myalgia syndrome caused by impure L-tryptophan supplements sold over-the-counter. Pharmaceutical grade L-tryptophan is currently available by prescription in the U.S. However the supplement 5-HTP can be bought over the counter and is a direct precursor to serotonin.

Adverse effects

General side effects

General side effects are mostly present during the first 1-4 weeks while the body adapts to the drug. Almost all SSRIs are known to cause either one or more of these symptoms:

- nausea
- drowsiness
- headache
- changes in weight and appetite
- changes in sexual behaviour (see the next section)
- increased feelings of depression and anxiety
- tremors
- increased sweating

It is not recommended to quit the medication because of the side effects, as they usually disappear after the adaptation phase and at the same time the antidepressive effects begin to show. However, despite being called general, the side effects and their duration is highly individual and drug-specific, so usually the treatment is begun with a small dose to see how the patient's body reacts to the drug. After that either the dose can be increased or the drug can be changed to some other if the side effects won't disappear or the patient feels they are too uncomfortable.

Suicidality

Over the years there have been many accusations by patients and their families of SSRI's causing suicidal ideation and behavior, but as there is little scientific support for this claim, judicial evidence is piling up that patients committed suicide after using SSRIs.[3] Manufactures of SSRIs historically have vehemently denied any such link and have always blamed the *disease* rather than the treatment. In 2003 the UKs Committee on Safety of Medicines banned [4] the use of paroxetine (known in that country as Seroxat) in the use of children due to evidence of increased harm and potentially suicidal behaviour. In early 2006 GlaxoSmithKline issued a press release[5] stating that new meta-analysis of their clinical trial data has revealed a statistically significant higher frequency of suicidality in patients treated with their SSRI, paroxetine (Paxil) than with placebo.

In the United States there is a required box warning for suicide risk in children but not for adults.

Sexual side effects

It is well known that the selective serotonin reuptake inhibitors (SSRIs) can cause various types of sexual dysfunction such as anorgasmia, erectile dysfunction, and diminished libido. Initial studies found that such side effects occur in less than 10% of patients, but those studies relied on unprompted reporting, so the frequency of such problems was underestimated. In more recent studies, doctors have specifically asked about sexual difficulties, and found that they are present in between 41%and 17% of patients. This dysfunction occasionally disappears spontaneously without stopping the SSRI, and in most cases resolves after discontinuance. In some cases, however, it does not; this is known as PSSD.

It is believed that sexual dysfunction is caused by an SSRI induced reduction in dopamine. Stimulation of postsynaptic 5-ht2 and 5-ht3 receptors decreases dopamine release from the Substantia Nigra. Sexual dysfunction caused by SSRI's has been shown to be mitigated by several different drugs. These include bupropion, buspirone, methylphendiate, mirtazapine, amphetamine, pramipexole and ropinirole.

Because of these sexual side effects, the SSRI fluoxetine (Prozac) was recently classified as a reproductive and developmental toxin by the Center for the Evaluation of Risks to Human Reproduction (CERHR), an expert panel at the National Institute of Environmental Health Sciences at the National Institutes of Health. The panel concluded "that there is sufficient evidence in humans that fluoxetine can produce reproductive toxicity in men and women as manifested by reversible, impaired sexual function, specifically orgasm."

Discontinuation syndrome

SSRIs are not addictive in the conventional medical use of the word (i.e. animals given free access to the drug do not actively seek it out and do not seek to increase the dose), but suddenly discontinuing their use is known to produce both somatic and psychological withdrawal symptoms, a phenomenon known as "SSRI discontinuation syndrome".[8] Compared to the withdrawal symptoms of such drugs as opiates, alcohol, or cocaine, these reactions are quite different and frequently less significant, although the prescribing labels acknowledge the possibility of "intolerable" discontinuation reactions and some patients are never able to completely withdraw from SSRI drugs. In Europe, SSRI manufacturers are not permitted to promote their products as "non-habit-forming", though in the U.S. this statement is used to promote SSRIs. SSRIs meet the World Health Organization definition of "addictive". Many physicians do not get informed consent at the time of initial prescription that covers the difficulties of later withdrawal from the drug, so this syndrome can be an unexpected barrier to patients, especially those who tried the drug in response to a specific crisis, who expected an easy withdrawal once their emotional situation stabilized. In addition, warnings to patients not to stop taking the drug without doctor's approval, while indicated, may lead to a reluctance to discontinue SSRI therapy.

General information about the SSRIs, their relative merits, and their side effects.

Prime Candidates

The SSRIs are particularly helpful in heading off depression in the early stages, before it becomes deeply rooted. Some studies suggest that SSRIs are ideal for those people with minor depressive illness -- much

better than tricyclics, such as imipramine, or the complication-prone MAOIs. The SSRIs are effective for major depression, too.

"Before taking Zoloft, I had a bad case of the blahs. Everything just seemed colorless. But now, sometimes I'll just lie in bed and rub the blanket between my fingers," says Sharon, 38. "It's not sexual, but my sensitivity is heightened. The feel-goodness goes right down into my bones."

Research seems to suggest that you can head off serious full-blown illness by taking an SSRI during the early stages of depression.

This doesn't mean that SSRIs are the only worthwhile antidepressant, of course. There is still a place for the older drugs. Research has shown that the older tablets (Tricyclics) are just as effective as the newer ones (SSRIs) but, on the whole, the newer ones seem to have fewer side-effects. A major advantage of the SSRIs is that they are not so dangerous if someone takes an overdose.

Researchers also note that the SSRIs don't work for 20 percent to 40 percent of depressed or anxious people who try them -- the same failure rate as for the older antidepressants.

Which SSRI Is Best?

Most experts agree that no single SSRI is better than the rest, despite Prozac's image as a miracle drug that not only cures depression but can make many healthy people "better than well". Each drug has a certain profile of its own particular side effects; some have markedly similar side effects, while others vary widely.

For example, Zoloft and Paxil don't last as long in the body as Prozac; the half-life of Zoloft is about 26 hours, and the half-life of Paxil is about 21 hours. ("Half-life" is the time it takes for a drug in the blood to decrease by half of its original dose.)

It's important to understand that all the SSRIs may cause nausea, headache, anxiety, dry mouth, insomnia, and a variety of sexual dysfunctions. But as mentioned, what makes Prozac less desirable is that it lingers in the body much longer than other SSRIs; up to six weeks after you stop taking the drug, traces of Prozac and its metabolites can still be found in your body. If you have a bad reaction to Zoloft or Paxil, symptoms last for a week or two. But side effects while taking Prozac can last for up to six weeks before all traces of the drug leave your body.

Of course, none of the SSRIs are any sort of wonder drug. They all have some side effects, although they are less severe than those of other antidepressants.

One of the biggest problems with these drugs is their cost. All of them are much more expensive than the generic versions of older drugs like MAOIs or tricyclics. Generic versions of the older drugs are available because their patents have expired.

No matter how wonderful a drug may be, if you can't afford it, it's not going to do you much good. The high cost of the SSRIs can be a real hardship for someone with no insurance, or whose insurance doesn't cover drugs. At about $2 to $3 per pill, the pharmacy bill can be overwhelming.

It's a problem for Mary, 28, whose health insurance covers all drugs except medications for mental health problems. "My psychiatrist is very aware of this problem," Mary explains. "He doesn't give me Zoloft alone because it would be too expensive. So he prescribes a smaller amount of Zoloft with desipramine (a less-expensive tricyclic)." The desipramine boosts the effects of Zoloft, and the combination costs less than a full dose of Zoloft alone.

SSRI Antidepressants, Suicidal Feelings and Young People

There is evidence of increased suicidal thoughts and behaviors and other side effects in young people taking antidepressants. So SSRI antidepressants, with the exception of Prozac, are not approved by the FDA for use in people under 18.

In fact, in 2004, the FDA ordered the strongest safety warning possible:

Antidepressants increase the risk of suicidal thinking and behavior (suicidality) in children and adolescents with major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of [Drug Name] or any other antidepressant in a child or adolescent must balance this risk with the clinical need.

Side Effects

The side effects of SSRIs are usually mild and manageable, although once in a while a sensitive person gets a severe reaction. Like most antidepressants, SSRIs may cause nausea, dizziness, or dry mouth, not to mention a range of sexual-function side effects, including decreased sexual interest (in men), increased sexual interest (in women), ejaculation problems, impotence, or menstrual changes.

During the first couple of weeks of taking them, you may feel sick and more anxious. Some of these tablets can produce nasty indigestion, but you can usually stop this by taking them with food. More seriously, as noted above, they may interfere with your sexual function. There have been reports of episodes of aggression, although these are rare.

The list of side effects looks worrying - there is even more information about these on the leaflets that come with the medication. However, most people get a small number of mild side-effects (if any). The side effects usually wear off over a couple of weeks as your body gets used to the medication. It is important to have this whole list, though, so you can recognize side effects if they happen. You can then talk them over with your doctor. The more serious ones - problems with urinating, difficulty in remembering, falls, confusion - are uncommon in healthy, younger or middle-aged people.

The most common side effects with Zoloft, launched in 1991, and Paxil, introduced in 1993, are insomnia, diarrhea, tremor, and drowsiness. If you get side effects while taking either of these, your doctor may switch you to Wellbutrin, as long as you don't have any of the conditions that might make you vulnerable to seizures with this drug (such as previous severe head injury or epilepsy). And like Prozac, Zoloft, Paxil, Celexa, Lexapro and other SSRIs, it can produce mild mania in some people with a genetic tendency in that direction.

Sexual dysfunction may occur in SSRI users from one to five percent according to the drug companies (although actual incidence of the problem may be much higher, critics charge -- as high as 40 percent).