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## **Long-Term Side Effects Surface With SSRIs**

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### **Insomnia, weight gain, sexual dysfunction emerge as problems affecting compliance.**

NEW YORK -- Physicians are seeing long-term side effects with selective serotonin reuptake inhibitors far in excess of what was expected from clinical trial data, Dr. Norman Sussman said at a psychopharmacology update sponsored by New York University.

If these particular side effects -- sleep disturbances, sexual dysfunction, and weight gain - - are problematic for patients, one of the newer non-SSRI antidepressants may be a better choice, he said. Of course, these drugs have their own particular side effect profiles.

When SSRIs first appeared a decade ago, their favorable side effect profile was a key selling point. They were clearly safer and easier to use than tricyclics and monoamine oxidase inhibitors and, above all, better tolerated by patients.

But experience has shown that some side effects are more common and problematic than initially expected, said Dr. Sussman, director of the psychopharmacology research and consultation service at Bellevue Hospital Center in New York.

Depression is a chronic, recurrent disorder, so long-term side effects actually may be more important than acute ones in terms of patient compliance and quality of life, and this has come to guide Dr. Sussman's choice of antidepressants.

Early-onset side effects may be responsible for rapid withdrawals from treatment, but some of the most troubling of these -- nausea, diarrhea, headache, and agitation -- will remit in 2-3 weeks.

A knottier problem is adverse effects that persist as long as the patient takes the medication, such as sexual dysfunction and sleep disturbances. Also particularly troubling are those, like weight gain, that don't even develop until late in treatment. "These are the ones that are not in the insert, which is based on short-term studies," Dr. Sussman said.

Significant insomnia affects 15%-20% of patients taking SSRIs, twice the rate with

placebo. Polysomnography has consistently found that these drugs cause activation during the night: In addition to insomnia, bruxism, sweating, and periodic limb movement are common. Vivid dreams and nightmares also occur. With ongoing treatment, increasing numbers of patients report lethargy and fatigue, he said.

"There are a lot of data showing that people who sleep poorly are more likely to relapse and that suicide risk is higher," he said.

Sleep problems often require concurrent medication: 22%-34% of patients taking SSRIs also are prescribed sedatives or hypnotics, Dr. Sussman said.

Sexual dysfunctions are among the most distressing SSRI side effects. Decreased libido and delayed or absent orgasm are the best known, but there are others, such as the "yawning-excitement syndrome." Patients experience sexual arousal when they yawn, often progressing to orgasm. "This is probably underreported. Patients often say, 'If you hadn't asked me, I wouldn't have mentioned it,'" he said.

Perhaps the most unexpected SSRI-related problem to emerge has been weight gain, which often begins only after several months of therapy. This side effect has not been shown to be frequent or severe in controlled studies but has been reported to occur in 18%-50% of patients in some open-label studies.

Because this runs counter to the image of the drug, many physicians and patients are unprepared to deal with it. "Some physicians tell patients, 'I can't understand why you're gaining weight -- you're on an SSRI,'" Dr. Sussman said.

Greg Keuterman, a spokesman for Eli Lilly & Co., manufacturer of Prozac (fluoxetine), declined to comment except to point out that "this is anecdotal evidence."

"We're approved by the FDA for long-term treatment of depression," he added.

Pfizer Inc., the maker of Zoloft (sertraline), and SmithKline Beecham Pharmaceuticals, the maker of Paxil (paroxetine), did not respond to requests for comment.

These observations do contrast with what the clinical trials submitted to the Food and Drug Administration by pharmaceutical companies show, Dr. Sussman said. It would be nice if these long-term side effects were studied in clinical trials comparing different antidepressants.

Some of the newer antidepressants are less likely to cause the types of long-term problems that lead patients to discontinue SSRIs, he said.

Of course, it is possible that unexpected side effects will emerge over the long term with these antidepressants as well, Dr. Sussman said.

With venlafaxine (Effexor), "the side effects are the same as with SSRIs: insomnia,

somnolence, lethargy and fatigue, and weight gain, but they are less intense." The new extended-dose formulation causes lower peak plasma levels, which appears to make the drug more tolerable. Notably less significant is nausea, which was a problem with the immediate-release form of venlafaxine, Dr. Sussman said.

Mirtazapine (Remeron) causes no gastrointestinal problems, sexual dysfunction, or insomnia over the long term, but difficulties are likely to occur early. Patients should be advised that while somnolence at the start of therapy may be "overwhelming," it usually lasts only 2-3 days. "You need to counsel patients to stick with it," he said.

Increased appetite and weight gain also may be marked in the first stage of therapy but will generally plateau after 2-3 months. "[Treatment with mirtazapine] works only if the patient trusts you that these effects are time limited and treatable," he said.

European trials of mirtazapine reported less trouble with initial weight gain and somnolence, perhaps because higher doses were used. "Most [clinicians] now agree on starting at 30 mg rather than 15 mg," Dr. Sussman said.

Nefazodone (Serzone) appears to cause little sexual dysfunction and minimal agitation and carries a low risk of weight gain. It enhances sleep quality and reduces awakenings. The most common side effects -- nausea, sedation, and dizziness -- are generally limited to the beginning of treatment and are dose related. "They diminish with each week of treatment," he said.

Physicians should be aware of the fact that patients who are switched directly from SSRIs to nefazodone experience a higher than expected rate of side effects.

Once-daily dosing in the evening can minimize daytime sedation and dizziness with nefazodone in patients who have been stabilized on the standard twice-a-day schedule, he said.

Bupropion (Wellbutrin) has been associated with headache, nausea, and dry mouth, but it is well tolerated by most patients, particularly in the long term. The sustained-release form appears to reduce seizure risk, which has been a concern with the drug. But bupropion still should not be given to patients who may be prone to seizures, Dr. Sussman said.