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Is There Any Risk of a Withdrawal Syndrome Associated with Abrupt Discontinuation of Selective Serotonin Reuptake Inhibitors?

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Question: Is there any risk of a withdrawal syndrome associated with abrupt discontinuation of selective serotonin reuptake inhibitors?

BY RENE A. ENDOW, PHARM.D., MARY A. GUTIERREZ, PHARM.D., AND MICHAEL Z. WINGOR, PHARM.D.

When the vast majority of depressed patients were treated with tricyclic antidepressants, significant concern developed among clinicians over potential withdrawal syndromes when abruptly discontinuing pharmacotherapy. Other than the possible recurrence of depressive symptoms, the major fear was emergence of a transient, but nonetheless distressing, "cholinergic rebound." This was characterized by excessive salivation and lacrimation, urinary frequency, diarrhea and other gastrointestinal complaints, as well as restlessness and sleep disturbances; it was thought to be a result of abruptly discontinuing a highly anticholinergic antidepressant that had been used at therapeutic doses for several months.

With the availability of the newer selective serotonin reuptake inhibitors (SSRIs), concern over a "cholinergic rebound" seemed unnecessary since these agents demonstrate little or no anticholinergic activity. However, a review of the literature indicates that there may be other withdrawal symptoms associated with discontinuation of the SSRIs. The time course and, perhaps to a lesser extent, the frequency of these symptoms appear to be correlated with the elimination half-lives of the agents. For a summary of the differences in half-lives, see Table 1.

Fluoxetine

Although fluoxetine has been available in the United States longer than any of the other SSRIs, reports of withdrawal symptoms associated with its discontinuation have only recently appeared in the literature; Berlin described three such cases.³ In one case, discontinuation of alprazolam accompanied the discontinuation of the patient's fluoxetine; therefore, the results are difficult to interpret. However, in the other two cases, only fluoxetine was involved. The more striking case was that of a 36-year-old man who had been treated with fluoxetine up to 40 mg per day. On

two separate occasions, his fluoxetine was abruptly discontinued; both times, within two days, he experienced brief "bursts" of dizziness or vertigo lasting a few seconds each and occurring numerous times each day. With resumption of the fluoxetine, the dizziness ceased within a few days.

The other patient, a 34-year-old man, even with gradual tapering of his 20 mg per day dosage of fluoxetine, experienced sensations of dizziness one week after stopping the drug. Again, the sensations lasted a few seconds each and occurred many times per day. Eight weeks after stopping the drug, the sensations were fully gone.

Sertraline

Two reports of withdrawal symptoms associated with discontinuation of sertraline can be found in the literature. A 46-year-old woman had her 100 mg per day of sertraline abruptly discontinued. Within two days, she reported fatigue, gastrointestinal complaints, insomnia, impaired memory, and flu-like symptoms. Addition of sertraline 25 mg daily resulted in rapid resolution of these complaints. A more gradual tapering resulted in similar, but milder, symptoms with each reduction in dosage.⁴

A 22-year-old man was tapered over a period of 8 weeks from 150 mg per day of sertraline. One day after his last dose of sertraline (50 mg), he complained of "electric shocks" that were primarily in the neck and chest and that progressed to his fingers and toes. They each lasted about a second and occurred every five to 10 minutes. The sensations diminished over time and completely stopped 13 weeks after discontinuation of the sertraline.⁵

Paroxetine

In 1993, the Committee on Safety of Medicines in the United Kingdom noted that discontinuation of paroxetine was associated with a mild and transient withdrawal syndrome consisting of dizziness, sweating, nausea, insomnia, tremor and confusion.⁶ Seven reports can be found in the literature describing such symptoms associated with paroxetine discontinuation. The total of 17 patients includes both males and females with an age range of 26 to 64 and typical daily doses of 20 to 40 mg.^{5,7-12}

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In general, the symptoms began within two to three days of discontinuation, whether abrupt or, at times, even following a taper and usually resolved over a period of one to two weeks. In addition, some patients complained of "electrical shocks" which would start in the upper body and move quickly down to the arms and hands; these would last only a few seconds but could occur constantly with motion. Interestingly, this complaint appeared to resolve more slowly than the other withdrawal symptoms.

Fluvoxamine

There are three reports, involving a total of 17 patients, in which discontinuation of fluvoxamine has been associated with withdrawal symptoms.¹³⁻¹⁵ The patients included both males and females with an age range of 25 to 56 and daily doses of 100 to 300 mg. The most frequent symptoms were dizziness/incoordination, headaches, nausea and irritability; in addition, confusion, memory problems, low energy, and weakness have been reported. These symptoms generally appear within one to two days of discontinuation, peak within five days, and dissipate within approximately two weeks.

Conclusion

There does appear to be some risk of a withdrawal syndrome following abrupt discontinuation of SSRIs; in fact, even tapering may be associated with such a risk, although perhaps a lesser one. The time course of this phenomenon appears to be somewhat correlated with the elimination half-life of the specific agent. However, other factors (e.g., binding affinities, variable effects on serotonin receptor sensitivity) may make any such predictions difficult. With respect to fluoxetine, the occurrence of a withdrawal syndrome may be rare due to the very protracted elimination of the drug and its active metabolite from the body; on the other hand, the phenomenon may not be noticed because the onset is so long after discontinuation of the drug.

The exact incidence is difficult to determine since most of the currently available information consists of

case reports; under such circumstances, we never quite know what the denominator of the proportion is. It is clear, however, in a number of cases that restarting the withdrawn agent resulted in an immediate and complete resolution of the withdrawal symptoms. If Ellison's¹⁶ estimate of a 5 percent incidence of the withdrawal syndrome is correct, it would be wise to slowly and carefully taper all patients (other than those in whom the potential risk of a slow taper outweighs the benefits) who have been treated with any of the SSRIs at a therapeutic dose for an extended period of time.

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Table 1

Elimination half-lives of the selective serotonin reuptake inhibitors^{1,2}

	Fluoxetine	Sertraline	Paroxetine	Fluvoxamine
Parent	1-6 days	26 hours	21-24 hours	15.6 hours
Metabolite	4-16 days ‡	2-4 days †	N/A	N/A

‡ half-life of the metabolite, norfluoxetine, appears to be dose-dependent

† the metabolite, desmethylsertraline, has minimal activity



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