Introduction

Antidepressant Discontinuation Syndrome: An Update on Serotonin Reuptake Inhibitors

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When selecting an antidepressant to treat a patient suffering from depression, a physician should consider the possibility of a discontinuation reaction. Discontinuation symptoms can occur when doses are frequently missed (intermittent noncompliance), upon abrupt cessation of treatment and, less often, during dosage reduction.

These symptoms have been reported with increasing frequency in the literature when the newer serotonin reuptake inhibitors (SRIs) are discontinued. The class of SRIs includes the serotonin selective reuptake inhibitors fluoxetine, fluvoxamine, paroxetine, sertraline, and citalopram (which is marketed in Europe but not the United States); the serotonin-norepinephrine reuptake inhibitor venlafaxine; and the tricyclic clomipramine.

A discontinuation reaction usually involves a cluster of adverse events that generally emerge within 24 to 72 hours after SRI discontinuation and that last, on average, 7 to 14 days. The phenomena, which can be distressing, include both somatic and psychological symptoms. Among the common somatic symptoms are disequilibrium (e.g., dizziness, vertigo), nausea and vomiting, and flu-like symptoms (e.g., fatigue, lethargy). The most frequently reported psychological symptoms are anxiety and/or agitation, crying spells, and irritability.

Symptoms occur more often when patients miss doses or abruptly stop taking an antidepressant than when they slowly taper the agent. Discontinuation reactions are more likely to occur or to become apparent during discontinuation of SRIs that have shorter half-lives than the extended half-life agent fluoxetine. Because discontinuation symptoms are being reported with increasing frequency in the literature, a panel of experts met recently to discuss whether an operationalized definition for a discontinuation syndrome was warranted.

The panel created a hypothetical definition of a proposed discontinuation syndrome. Hallmark features of this syndrome are:

- It is not attributable to other causes.
- It is emergent upon abrupt discontinuation, frequent noncompliance (missed doses), and, less often, after dose reduction.
- It is generally mild and short-lived but can be distressing.
- It can be reversed by the reintroduction of the original medication or one that is pharmacologically similar.
- It is minimized by a slow taper or by using a drug that has an extended half-life.

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Michel Lejoyeux, M.D., Ph.D., in a review of the literature, noted that discontinuation reactions occur with most antidepressants and suggested that physicians directly question patients about symptoms that emerge when antidepressant therapy has ended.

Peter Haddad, M.D., noted that the data on antidepressant discontinuation are drawn mainly from anecdotal case reports, spontaneous reports of adverse drug reactions monitored by national surveillance organizations, and a few clinical trials. He also noted that the vast majority of the reports of discontinuation symptoms with the serotonin selective reuptake inhibitors involve paroxetine and the fewest are for fluoxetine.

The panel suggested several potential mechanisms of action. Possible mechanisms for SRI discontinuation reactions include a decrease in available synaptic serotonin in the face of down-regulated serotonin receptors, secondary effects on other neurotransmitters, and biological or cognitive sensitivity in individual patients. In addition, for paroxetine, the symptoms of discontinuation may in part be mediated by a cholinergic rebound effect.

A. H. Young, M.D., Ph.D., in a survey of physicians in the United Kingdom, has found that many general practitioners are unaware that patients may have experienced withdrawal reactions.

Eric Kaplan, M.D., pointed out that noncompliance with therapy is common and thus often leads to discontinuation symptoms. He suggested that physicians could decrease the likelihood of intermittent noncompliance, characterized by missed doses, by spending more time educating patients about their therapy.

Jerrold R. Rosenbaum, M.D., and John Zajecka, M.D., suggested strategies for the clinical management of SRI discontinuation. If the discontinuation syndrome is acute, the original antidepressant dose should be reintroduced and the rate of taper slowed. Gradual taper and the use of an antidepressant with an extended half-life are other methods for minimizing discontinuation symptoms.

While discontinuation symptoms are generally mild and transient, the syndrome can be troublesome, leading to missed work and reduced productivity. It can also be mistaken for new physical illness or the return of the original depression. Misdiagnosing symptoms may lead to costly, unnecessary testing and treatment. Thus, depression treatment guidelines should include information about drug discontinuation, and health care professionals should be educated about the management of symptoms that often accompany SRI discontinuation.