Clinical Management of Antidepressant Discontinuation

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To minimize the symptoms of antidepressant discontinuation, gradual tapering is necessary for all serotonin reuptake inhibitors (SRIs) except fluoxetine, which has an extended half-life. Agents with shorter half-lives such as venlafaxine, fluvoxamine, and paroxetine should be tapered gradually. Discontinuation symptoms, which frequently emerge after abrupt discontinuation or intermittent noncompliance and, less frequently, during dose reduction, are generally mild, short-lived, and self-limiting but can be distressing and may lead to missed work days and decreased productivity. The symptoms may be somatic (e.g., dizziness and light-headedness; nausea and vomiting; fatigue, lethargy, myalgia, chills, and other flu-like symptoms; sensory and sleep disturbances) or psychological (anxiety and/or agitation, crying spells, irritability). Mild symptoms can often be treated by simply reassuring the patient that they are usually transient, but for more severe symptoms, it may be necessary to reinstitute the dosage of the original antidepressant and slow the rate of taper. Symptoms of discontinuation may be mistaken for physical illness or relapse into depression; misdiagnosing the symptoms may lead to unnecessary, costly tests and treatment. Thus, health care professionals need to be educated about the potential adverse effects of SRI discontinuation.

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Discontinuation symptoms occur in about one third of patients who stop serotonin reuptake inhibitor (SRI) therapy.[1] The most common symptoms are physical and may include feelings of disequilibrium (e.g., dizziness, light-headedness); nausea and vomiting; flu-like symptoms like fatigue, lethargy, myalgia, and chills; and sensory and sleep disturbances. However, psychological symptoms such as anxiety and agitation, crying spells, and irritability have also been noted.[2] Paying attention to the time frame of symptoms that emerge upon antidepressant discontinuation or when doses are missed will aid in the diagnosis of discontinuation symptoms. These symptoms usually commence within 24 to 72 hours of SRI discontinuation and last from 7 to 14 days. Reassurance is often the only treatment needed, but for cases where symptoms are particularly bothersome or severe, it may be necessary to reinstitute the antidepressant dose and slow the rate of taper. The risk of discontinuation events can be minimized by tapering all SRIs except for fluoxetine, which has an extended half-life.

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IMPORTANCE OF DIAGNOSIS

While treatment guidelines for depression provide advice on diagnosing depression, starting treatment, and establishing a maintenance regimen, little attention has been given to discontinuing treatment. As a result, few physicians are concerned with therapy termination, and many often fail to recognize and/or diagnose this cluster of symptoms as an antidepressant discontinuation event. Thus, the symptoms that accompany discontinuation are often either mistaken for the flu or a depressive relapse. Patients who experience discontinuation events are sometimes given costly, unnecessary diagnostic tests. For example, one patient with discontinuation dizziness was examined by a neurologist and otorhinolaryngologist, had magnetic resonance imaging of the head, and underwent tests for Lyme disease.[3] Other patients have been given complete physical examinations[4] or laboratory tests.[5] Psychiatric symptoms of discontinuation such as anxiety and agitation, crying spells, or irritability are also sometimes misdiagnosed as a depressive relapse and, as a result, the patient may resume antidepressant treatment for up to 1 year. Some patients who experience these psychiatric symptoms when they stop treatment or miss several doses of their antidepressant may become reluctant to continue treatment in the mistaken belief that they have become ad-

dicted to the antidepressant. Or, if the depression recurs several years later, they may not present for treatment because of the memory of adverse discontinuation events. Patients may also mistakenly conclude that symptoms of discontinuation are evidence of the need for continued treatment or continue with treatment to which they are only partially responsive because of adverse discontinuation events.

Untreated depression can be costly to society in terms of lowered productivity as well as increased morbidity and mortality. Although the symptoms of SRI discontinuation are seldom medically dangerous, they have an adverse effect on many patients' quality of life and have led to missed work days, lowered productivity, and higher medical costs. In one study,[6] 5 of 14 patients who discontinued fluvoxamine treatment took at least 1 day off from work, and 3 sought medical attention locally. Another patient was confined to bed and absent from work for 3 days because of severe dizziness associated with paroxetine discontinuation.[7] Frost and Lal[8] reported on two patients who had difficulty walking because of "electric shocks" and dizziness when paroxetine treatment was ended and one patient whose dizziness caused him to lose control of the steering wheel of his car after sertraline was stopped. Discontinuation events may also increase health care costs in terms of extra visits to physicians and hospital emergency rooms.

When patients present with new symptoms, particularly in an emergency room, they should be routinely asked if they have missed or forgotten to take any doses of medication, if the dosage has been changed recently, or if they have stopped taking any medication within the past several days. These questions are important for physicians in all specialties to ask, since, for example, an infant whose mother discontinued antidepressant treatment while breast-feeding experienced discontinuation symptoms.[9] Symptoms sometimes appear when patients miss several antidepressant doses, particularly of the shorter-acting SRIs such as paroxetine, sertraline, and venlafaxine for which discontinuation symptoms have been observed in as few as 12 to 24 hours after a missed dose.

Symptoms of antidepressant discontinuation can be differentiated from symptoms of depressive relapse by the time frame. Discontinuation-emergent symptoms usually begin within 1 to 3 days after antidepressant treatment is stopped, while signs of relapse are unlikely to become evident for 2 to 3 weeks. Withdrawal symptoms are unlikely to occur in patients who have been treated with SRIs for fewer than 7 weeks.[2] In addition, discontinuation events will remit within a couple of days after the antidepressant is reinstituted or one that is pharmacologically similar is substituted. Patients who have a history of antidepressant noncompliance, who have experienced discontinuation symptoms in the past, or who have treatment-emergent anxiety are at highest risk for experiencing discontinuation phenomena.

Table 1. Strategies to Manage Discontinuation Events

- Reassure the patient that the symptoms are likely to be short-lived and mild
- For acute symptoms, reinstitute the dosage and slow the rate of taper
- Gradually taper all serotonin reuptake inhibitors except fluoxetine
- Treat with agent with an extended half-life, e.g. fluoxetine

CLINICAL MANAGEMENT

Strategies to treat discontinuation symptoms are listed in Table 1. They include providing reassurance to the patient if symptoms are mild, slowing the rate of taper, and, for acute symptoms, reinstituting the antidepressant dosage or substituting another antidepressant that has a similar pharmacologic profile.

Provide Reassurance

Because discontinuation symptoms are usually mild and transient, many patients need only reassurance to help them cope with the adverse events. Results from studies on the contribution of cognitive-behavioral factors to the occurrence of discontinuation phenomena may lead to specific therapeutic interventions. For example, Otto et al.[10] found in a study of discontinuation of benzodiazepine patients that 76% of patients who received a combination of slow tapering and cognitive-behavioral therapy, as opposed to 25% of the group who received slow tapering alone, remained benzodiazepine-free at the 3-month follow up. The patients who received cognitive-behavioral therapy were informed about possible discontinuation symptoms and taught specific behaviors to cope with anxiety. The two groups experienced the same biological perturbations, but the group who had cognitive-behavioral therapy had their coping skills enhanced, which suggests that educational interventions can be helpful in successful antidepressant discontinuation. Often, it will be sufficient to tell the patient that the symptoms are likely to disappear within a few days.

Patients who have been responding well to SRI therapy and present with new symptoms such as dizziness and light-headedness, nausea and vomiting, sensory and sleep disturbances, flu-like symptoms, anxiety/agitation, crying spells, or irritability should be asked if they have forgotten or missed any doses. For example, they may have left their medication at home when they went on vacation. Since intermittent noncompliance can lead to discontinuation events, patients may need to be reminded frequently about the importance of taking every dose.

Slow the Rate of Taper

When a patient successfully completes treatment, the agents with shorter half-lives such as fluvoxamine, paroxetine, sertraline, and venlafaxine should be routinely tapered slowly to the minimum therapeutic dose or often

Table 2. Suggested Rate of Taper for SRIs After Successful Treatment*

SRI	Rate of Taper [a] (mg/d)	Minimum Therapeutic Dose (mg/d)	Usual Final Dose (mg/d)
Fluoxetine	…[b]	20	20
Fluvoxamine	50	100	25–50
Paroxetine	10	20	5–10
Sertraline	50	50	25–50
Venlafaxine[c]	25	75	25–50

*Abbreviation: SRI = serotonin reuptake inhibitor.
[a]Dose should be lowered every 5 to 7 days.
[b]Gradual taper generally unnecessary for fluoxetine.
[c]Manufacturer recommends taper for anyone who has been treated for ≥ 1 week.

below it (Table 2). The rate of taper should depend on a number of factors, including the pharmacologic profile of the specific drug, the current dose, and the duration of treatment. Paroxetine should be tapered slowly; the rate of taper should depend on the patient's comfort and discontinuation symptoms. The final dose may be below the minimum therapeutic dose. For example, a patient who has been taking 60 mg/day of paroxetine for 12 months should be tapered by 10 to 20 mg/week. If discontinuation symptoms appear while the patient is taking the recommended minimum therapeutic dose, it may be necessary to continue to half the dose until the patient is taking 5 mg/day. Similarly, it is often necessary for the final dose of fluvoxamine or sertraline to be lower than the starting dose.

Sometimes discontinuation symptoms persevere even if the SRI is being tapered slowly.[11,12] In that case, it may be necessary to reinstitute the original antidepressant dose and further slow the rate of taper. However, symptoms are occasionally so severe that patients are unable to discontinue antidepressant treatment.[13] If the symptoms continue, one additional strategy is to substitute fluoxetine, which has an extended half-life, for the original agent, as illustrated in one case in which the severe dizziness experienced by one patient after paroxetine discontinuation was alleviated when fluoxetine therapy was begun.[7]

Patients may also experience discontinuation symptoms when they are switched from one agent to another for lack of efficacy. Thus, the two drugs should be titrated, upward and downward, against the adverse effects. If the drugs have similar pharmacologic profiles, it is usually possible to reduce the dose of the initial drug quickly and simultaneously add the new medication.

FUTURE NEEDS

Guidelines for the treatment of depression should include advice on discontinuing SRI therapy. It is particularly important that information about the possibility of discontinuation reactions be included in patient educational materials designed for primary care physicians, who often treat depression. Medical students, psychologists, nurses, and pharmacists should also be aware that patients may experience discontinuation symptoms when they stop SRI treatment since patients often bring complaints to these nonphysicians.

Patient education should be provided by physicians and other mental health professionals. When antidepressant treatment is begun or shortly after the patient has started to respond to an antidepressant, he or she should be educated about the importance of taking every dose and about the risk of discontinuation symptoms if treatment is stopped abruptly or interrupted regularly.

Additional clinical strategies to treat antidepressant discontinuation events may become evident after more data is gathered about the phenomenon. For example, little research has been published on the percentage of paroxetine-, sertraline-, or venlafaxine-treated patients who experience discontinuation reactions. Ideally, every antidepressant should be included in a double-blind, placebo-controlled study of discontinuation events as part of the phase 3 evaluations during the Food and Drug Administration (FDA) approval process. Basic studies are also necessary to establish the mechanism of action of the discontinuation phenomena and the specific risk factors for discontinuation symptoms. In addition, specific groups such as the young or the elderly or patients who become anxious or nauseated when they start therapy should be studied to ascertain whether they may be at greater risk for suffering through a discontinuation reaction.

CONCLUSION

When initiating antidepressant therapy for a patient, a physician must consider the eventual risk of a discontinuation syndrome. While patients may experience discontinuation reactions when they stop therapy with any SRI, discontinuation-emergent symptoms have been reported much less frequently for fluoxetine than the short half-life SRIs, paroxetine, sertraline, fluvoxamine, and venlafaxine. Patients who are discontinuing therapy need to be tapered gradually from all SRIs except fluoxetine; sometimes the final dose will be lower than the minimum therapeutic dose. The extended half-life of fluoxetine may provide protection against discontinuation symptoms, and patients who are unable to tolerate these discontinuation events may benefit from a switch to fluoxetine.

Drug names: fluoxetine (Prozac), fluvoxamine (Luvox), paroxetine (Paxil), sertraline (Zoloft), venlafaxine (Effexor)

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Discussion

Dr. Haddad: Physicians routinely ask patients to list the medications they are taking, but, when someone presents with acute symptoms, the physician seldom asks, "Are there any medications that you have stopped taking in the last few days?" That question should also be routine.

Dr. Schatzberg: The immediate drug history is extremely important. It should include changes in medication as well as those that have been discontinued. We don't teach residents—particularly those who are working in emergency rooms—to ask these questions.

Dr. Rosenbaum: For example, in August a patient was hospitalized at my medical center to rule out a myocardial infarction. It turned out that the symptoms occurred in the context of venlafaxine discontinuation. When venlafaxine was reintroduced, the symptoms abated. The patient was ultimately switched to fluoxetine.

Dr. Young: Serotonin selective reuptake inhibitors (SSRIs) are the first-line treatment for premenstrual dysphoric disorder (PMDD), but many women want to discontinue taking medication during certain parts of the menstrual cycle. Thus, my colleagues and I tend to prescribe fluoxetine for PMDD because it is more robust during discontinuation.

Dr. Haddad: Discontinuation symptoms are often misdiagnosed. Einbinder [Am J Psychiatry 1995;152:1235] described a young woman who was sent to a neurologist and an otorhinolaryngologist, had magnetic resonance imaging of her head, and was tested for Lyme disease because of dizziness that occurred in the context of SSRI discontinuation. Some patients miss a few doses and then drop out of treatment when they experience discontinuation symptoms. Symptoms develop in other patients when the antidepressant is stopped abruptly at the end of treatment. When depression recurs several years later, the patient is unwilling to begin treatment because the discontinuation phenomena after the first episode were unpleasant.

Dr. Young: To avoid discontinuation symptoms, my colleagues and I educate the patients about possible symptoms and reassure them when the symptoms occur that they will be short-lived. We titrate the dose down against the discontinuation syndrome. The rate of titration depends on the pharmacologic characteristics of the drug. Thus, paroxetine is titrated more gradually than fluoxetine.

Dr. Schatzberg: I decrease the paroxetine dose about 10 mg/day every 5 to 7 days.

Dr. Young: The crucial period is at the end when patients are taking 10 mg/day of paroxetine. I tend to decrease the paroxetine dose to 5 mg/day.

Dr. Haddad: The SSRIs, except for paroxetine, can usually be discontinued when the patient is taking the minimum therapeutic dose, but the daily paroxetine dose needs to be tapered to below 20 mg, i.e., the smallest tablet that the manufacturer makes.

Dr. Kaplan: Some patients have discontinuation symptoms when they stop the minimum therapeutic dose of sertraline or fluvoxamine.

Dr. Young: Any condition that makes long-term patient compliance less likely is something that has profound pharmacoeconomic costs and costs in terms of human suffering.