SSRI discontinuation syndrome

Awareness as an approach to prevention

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PREVIEW

In recent months, as the United States has struggled with the effects of terrorism, economic stress, and job layoffs, prescriptions of antidepressants have been on the rise. Even before this increase, compliance in the use of antidepressants, including the selective serotonin reuptake inhibitors (SSRIs), was compromised. Discontinuation syndrome, a cluster of symptoms caused by sudden cessation of SSRI use, is experienced by up to 25% of patients who abruptly quit taking these agents. Here, Dr Ditto discusses the incidence, onset, duration, and severity of these symptoms and offers ways to prevent unnecessary medical workups yet facilitate early recognition of discontinuation syndrome.

A 57-year-old man from Boston travels to Barcelona with his wife. He has a history of depression, hypertension, and type 2 diabetes and takes paroxetine hydrochloride, metoprolol, and metformin hydrochloride. With a 2-week supply of his medications on hand, he arrives in Barcelona and enjoys his usual state of health during the trip. His return flight to Boston is delayed 14 hours, and he and his wife stay in a hotel overnight. During the flight the next morning, he experiences headaches, anxiety, restlessness, and numbness and tingling in his hands and face. The symptoms persist when he arrives at an emergency department in Boston, where his evaluation results are unremarkable.

Symptoms of SSRI discontinuation syndrome are generally mild and short-lived. However, as this hypothetical case illustrates, the phenomenon may be mistaken for physical illness (eg, myocardial infarction, pulmonary emboli, transient ischemic attack) or relapse into depression and may prompt some patients to seek costly emergency department visits and unnecessary medical workups. Once the syndrome has been identified, healthcare providers can reassure most patients that their symptoms will abate when the antidepressant is restarted.

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Use of SSRIs

SSRIs are considered the medications of choice for a wide range of psychiatric disorders, including depression, anxiety, posttraumatic stress disorder, bulimia, premenstrual dysphoric disorder, obsessive-compulsive disorder, dysthymia, and other problems such as irritable bowel syndrome. These agents include fluoxetine hydrochloride (Prozac, Sarafem), paroxetine hydrochloride (Paxil), fluvoxamine maleate (Luvox), sertraline hydrochloride (Zoloft), and citalopram hydrobromide (Celexa).

A major reason for such widespread use of SSRIs is their safety and tolerability relative to the agents previously used, such as tricyclic antidepressants (TCAs), which are known for their anticholinergic side effects and lethality in overdose (as a result of hypotension, cardiac arrhythmia, or seizure). However, one often overlooked problem with SSRIs is discontinuation syndrome, a constellation of symptoms that can occur as a result of intermittent noncompliance, abrupt

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Table 1. Symptoms of SSRI discontinuation syndrome

Psychiatric
Anxiety
Crying spells
Insomnia
Irritability
Mood lability
Vivid dreams
Gastrointestinal
Nausea
Vomiting
Neurologic
Dizziness
Headache
Paresthesia
Motor
Dystonia
Tremor
Somatic
Chills
Fatigue
Lethargy
Myalgias
Rhinorrhea

SSRI, selective serotonin reuptake inhibitor.

Information from Schatzberg et al,[2] Black et al,[3] Haddad,[4] and Richelson.[5]

cessation of treatment and, less often, tapering of the SSRI dose.

Definition

Malcolm Lader[1] suggested that a discontinuation syndrome should be "a well-defined syndrome with predictable onset, duration, and offset of action containing psychological and bodily symptoms not previously complained of by the patients. It can be suppressed by the reinstitution of discontinued medication." Several researchers have proposed criteria for an SSRI discontinuation syndrome.[2,3] Despite the lack of a definition based on consensus criteria for the syndrome, patients who have disequilibrium, flulike symptoms, and sleep or sensory disturbances within 24 to 72 hours after discontinuing SSRI use are likely to be experiencing a discontinuation reaction. This is especially true if the symptoms cannot be ascribed to other causes and are alleviated by reintroduction of the medication.

Although the symptoms of discontinuation syndrome are not dangerous, they can be uncomfortable and distressing to patients. They include psychiatric, gastrointestinal, neurologic, motor, and somatic manifestations (table 1).[2-5] Dizziness is the most commonly reported symptom and may also be described as lightheadedness, faintness, vertigo, ataxia, or a "spaced out" sensation that markedly worsens with movement.[3,6]

Discontinuation symptoms usually begin within 1 to 3 days after abrupt cessation of SSRI use and can be relieved within 24 hours by restarting anti-depressant therapy. Untreated, however, these symptoms can last from 1 to 3 weeks.[2] Although most discontinuation reactions are mild and short-lived, the symptoms can be mistaken for physical illness or relapse into the treated illness, thereby promoting unnecessary long-term treatment.[7] Symptoms caused by an abrupt discontinuation of SSRI therapy during hospitalization may confound the ongoing assessment of mental status changes or physical findings of a comorbid acute illness (eg, meningitis, stroke, myocardial infarction)[8] and may result in unneeded and costly diagnostic evaluations.

Incidence and frequency

Given the diverse manifestations of SSRI discontinuation syndrome and the confounding comorbidities of many patients who receive these agents, the establishment of incidence, risk, and predisposing factors has been a challenge. The incidence reported can vary widely. There are no significant associations with age, sex, or diagnostic grouping.[6] Since most discontinuation reactions are self-limiting and usually go unrecognized and unreported by

both patient and physician, the reported reactions are likely to be marked underestimations of the true incidence.

The likelihood of discontinuation syndrome is associated with the duration of SSRI treatment; reactions rarely occur in patients who receive treatment for less than 6 to 8 weeks.[3,4,6] Although discontinuation symptoms can develop during a slow taper of an antidepressant medication, they occur more often when a patient abruptly stops or misses several doses of the medication.[2,6]

The variation in frequency of discontinuation reactions among the SSRIs can be partly explained by various pharmacokinetic factors, such as the half-life of the parent drug, the presence of active metabolites, and autoinhibition,[4,5,9,10] which results in a nonlinear elimination curve (especially with paroxetine and fluoxetine). Among the SSRIs, the potency of inhibition of serotonin reuptake and the affinity for muscarinic blockade (both greatest for paroxetine) are pharmacodynamic factors that may influence the variation and severity of dis-

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Table 2. Parameters for discontinuation phenomena among several classes of antidepressants

Antidepressant	Plasma half-life (hr)[10]	Frequency of discontinuation symptoms[5]	Potency of inhibition of serotonin reuptake[5]	Affinity of muscarinic blockade[5]
Citalopram HBr (Celexa)*	30-35	–/+	+	–/+
Clomipramine HCl (Anafranil)†	14-28	+++	+	+++
Fluoxetine HCl (Prozac, Sarafem)*	48-72	–/+	++	–/+
Fluvoxamine maleate (Luvox)*	12-15	++	+	–
Mirtazapine (Remeron)‡	20-40	–/+	–	+
Nefazodone HCl (Serzone)§	2-5	–/+	–/+	–
Paroxetine HCl (Paxil)*	20-24	+++	+++	++
Sertraline HCl (Zoloft)*	24-48	+	++	+
Venlafaxine HCl (Effexor)‡	5-7	–/+	–/+	–

–, none; –/+, negligible; +, mild; ++, moderate; +++, strong.
*Selective serotonin reuptake inhibitor (presynaptic transporter blocker).
†Tricyclic antidepressant (for reference).
‡Serotonin-norepinephrine reuptake inhibitor.
§Serotonin receptor blocker (postsynaptic).

Information from Schatzberg et al,[10] and Richelson.[5]

Symptoms of SSRI discontinuation syndrome can mimic upper respiratory infection, benign paroxysmal positional vertigo, radiculopathy, or the effects of certain medications.

continuation reactions (table 2).[4,5]

Discontinuation symptoms are more likely to occur in patients who take an SSRI with a shorter half-life than in patients taking an SSRI with a longer half-life and long-acting metabolites. The SSRIs implicated most often are paroxetine and fluvoxamine, which have a short half-life and no active metabolites. The rates of symptom occurrence reported for paroxetine are comparable with those reported for TCAs and monoamine oxidase inhibitors (MAOIs).[4]

Discontinuation symptoms have been reported less often for sertraline,[6] which has a long half-life (2 to 4 days) and a minimally active metabolite, desmethylsertraline.[11] The symptoms may occur less often with fluoxetine because of its long half-life (2 to 3 days) and the long elimination half-life (7 to 9 days) of its active metabolite, norfluoxetine.[11] Discontinuation of fluoxetine is also associated with a late and more gradual onset of symptoms of milder severity, sometimes occurring more than 1 week after use of the drug has been stopped.[9]

Several anecdotal reports of symptoms that followed citalopram discontinuation have also been recorded.[4,12] The elimination half-life of citalopram is 30 to 35 hours; citalopram's metabolites are present in much smaller concentrations, are much less potent, and do not enter the brain as readily as the metabolites of other SSRIs, and they do not appear to play a significant role in its clinical action.[12]

Other antidepressants

Discontinuation syndromes have also been reported among related classes of antidepressants. These agents include the cyclic antidepressants trazodone hydrochloride (Desyrel) and nefazodone hydrochloride (Serzone) as well as the serotonin-norepinephrine reuptake inhibitors venlafaxine hydrochloride (Effexor) and mirtazapine (Remeron).[2] Earlier onset of discontinuation symptoms—sometimes within 24 hours of a missed dose—may be associated more with venlafaxine than with paroxetine or fluoxetine. Anecdotal reports of discontinuation symptoms exist for nefazodone (its metabolites have a half-life of 2 to 18 hours) and for mirtazapine. Discontinuation of therapy with TCAs and MAOIs also can precipitate a similar profile of symptoms.

Differential diagnosis

At a time when US hospitals are cutting staff, overworked residents in outpatient clinics and in emergency departments may miss this very treatable syndrome. As a result, costly tests may be ordered that medical facilities can ill afford. When the diagnosis is missed in inpatient units, hospital stays become longer and more expensive.

Diagnosis of SSRI discontinuation syndrome is complicated by the fact that symptoms can mimic upper respiratory infection, benign paroxysmal positional vertigo, radiculopathy, or the effects of certain medications. Presentation of discontinuation phenomena also may be confounded or exacerbated by the presence of substance abuse, dehydration, or concurrent physical illness.

Careful history taking can help physicians discriminate between

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iscontinuation symptoms and ther medical concerns, a relapse f depressive symptoms, the emer- ence of psychosis, and rebound henomena. A detailed descrip- ion of symptoms and a review f organ systems can elucidate ossible medical causes. Because atients are not always forthcom- ng about medication noncompli- nce, the evaluator should ask pecifically about any changes in he medications that a patient as been taking. The patient hould be asked whether refills ave been appropriately obtained, doses have been missed, pills ave been split to make them last onger, and side effects (eg, sexual dysfunction) have affected the patient's compliance with antidepressant use. Potential drug interactions should also be noted.

A report of the patient's use of alcohol and illicit substances should be elicited. These substances may influence the presentation of discontinuation phenomena, and certain potentially dangerous substance withdrawal syndromes require different management. For example, alcohol abuse, distinguished by its dysautonomia (ie, tachycardia, diaphoresis, and elevated blood pressure), requires detoxification.

Distinguishing discontinuation reactions from a return of psychiatric symptoms is essential. Discontinuation symptoms have a typical onset of 1 to 3 days after use of the antidepressant is stopped. By comparison, rebound phenomenon (a return of some of the symptoms of depression) or a full depressive relapse usually takes 2 to 3 weeks to become evident and does not remit within 24 hours of restarting the antidepressant.

A patient who has SSRI discontinuation syndrome can be reassured that the symptoms are likely to be mild and short-lived.

Because discontinuation phenomena arise acutely and can mimic certain emergent medical events (eg, myocardial infarction, stroke, pulmonary embolism), further evaluation, such as an electrocardiogram and basic serum chemistry testing, may occasionally be necessary to rule out medical illness. With a high index of suspicion for antidepressant discontinuation symptoms and a presentation consistent with these phenomena, the evaluation and appropriate reinitiation of an antidepressant can be undertaken with minimal need for further medical workup or extended hospitalization.

Management

A patient who has SSRI discontinuation syndrome can be reassured that the symptoms are likely to be mild and short-lived. If symptoms are acute, relief is usually achieved within 24 hours by restarting the SSRI at the same dose the patient was taking when the medication was discontinued. A slow taper can then be instituted over several weeks. If the patient continues to have difficulty, even with a slow taper, cross-tapering with an agent that has an extended half-life may prevent discontinuation symptoms during the taper.[8]

Prevention

Because adherence to the medication regimen is necessary to minimize the occurrence of discontinuation phenomena, education about the natural course of the illness for which the SSRI has been prescribed and about medication compliance is crucial. This education begins with establishment of rapport and negotiation of physician-patient differences in beliefs and expectations about the illness and its treatment.

Treatment options that may supplement medication and enhance compliance (eg, psychotherapy, support groups) should be discussed with the patient, thus minimizing the likelihood of frustration and premature discontinuation. Prior antidepressant trials, the cost and side effects of medication, the complexity of

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preexisting medical regimens, and the chronicity of the illness are integral to a discussion about the patient's expectations and willingness to continue treatment as prescribed.

In particular, physicians should explain that a full response to medication might take up to 6 weeks. Patients should be advised to continue taking their medication—even after they begin to feel better—to maximize their ability to achieve a full response, avoid reemergence of symptoms or a full relapse, and avoid discontinuation symptoms that can occur when doses are missed or the antidepressant is stopped abruptly.

Patients also should be informed that before they stop taking an antidepressant, they should contact their physician, who can guide a slow taper of the antidepressant dose. On follow-up visits, an evaluation of symptom relief, side effects, missed doses, and substance use should be done, as well as an assessment of changes in job performance and in family and social relationships.

Patients often wonder how long they will need to take an antidepressant. Physicians should explain that antidepressant therapy needs to continue for 6 to 12 months to minimize the chance of relapse. They also should explain that maintenance treatment for 1 year to several years may be appropriate for a patient who has had multiple episodes of depression, a severe recurrent course of depression, or an early onset of depression (ie, before age 20 years), or has a first-degree relative with recurrent major depression or bipolar disorder.[4]

Ongoing education and discussion about a patient's experiences of the illness and its treatment help to reinforce both the treatment alliance and medication compliance. In addition, the patient will be less likely to suddenly stop taking the medication and experience discontinuation symptoms.

Summary

Although SSRIs are widely used and generally considered safe, an abrupt cessation of SSRI use may result in a discontinuation syndrome that can mimic serious illness and can be distressing and uncomfortable. Several pharmacokinetic and pharmacodynamic factors influence the frequency and onset of these symptoms. Rapid identification of SSRI discontinuation syndrome and reinstitution of the medication can provide rapid symptom relief. Ongoing education and discussion about the illness and its treatment can promote medication compliance and thus minimize the potential for sudden cessation of the SSRI, the uncomfortable experience of discontinuation symptoms, and unnecessary medical expenditures. **PGM**

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