The Nature of the Discontinuation Syndrome Associated With Antidepressant Drugs

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A common phenomenon accompanying treatment with nearly every major class of antidepressant is the emergence of the discontinuation syndrome in some patients. It is seen most frequently after the abrupt cessation of agents with shorter half-lives. The term *withdrawal* has been used in the past; however, the distinctions between discontinuation symptoms and drug withdrawal are clear. Thus, the use of proper terminology when discussing this phenomenon with patients will help to alleviate concerns and stop the spread of common misperceptions. In addition, awareness of the unique nature of discontinuation effects and a grasp of the typical time frame of their emergence can assist in distinguishing between discontinuation syndrome and relapse. As a result, it is vital that both patients and their relatives, especially caregivers, be provided with adequate education and a realistic and objective appraisal of expected outcomes upon initiation of antidepressant treatment.

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Abrupt termination of treatment with serotonin reuptake inhibitors (SRIs) can result in a phenomenon referred to as the SRI discontinuation syndrome, which is characterized by the rapid onset of 1 or more symptoms, such as anxiety, crying, dizziness, headache, increased dreaming, insomnia, irritability, myoclonus, nausea (with occasional vomiting), paresthesias (including "electrical sensations"), and tremor.[1,2] Discontinuation syndromes are specific neither to newer SRIs nor to SRIs in general—similar phenomena have been reported with at least 21 different antidepressants over the past 5 decades, including SRIs, tricyclic antidepressants (TCAs) and related compounds, monoamine oxidase inhibitors (MAOIs), and others.[1,3–6] In fact, the highest relative rates of discontinuation symptoms have been observed with the TCA clomipramine (21.5% to 100%),[1] although these rates have not been confirmed in head-to-head comparisons. Estimates of the prevalence of the SRI discontinuation syndrome vary widely due to a lack of large, well-controlled studies as well as uniform diagnostic criteria and assessment instruments. In addition, the incidence of discontinuation phenomena differs depending on the SRI: rates vary from as low as almost 0% for fluoxetine to as high as 17.2% to 78% for the SRIs with shorter half-lives.[7,8]

Despite its prevalence, the SRI discontinuation syndrome is underrecognized by both clinicians and patients. As a result, a general lack of patient education exists regarding this condition. In addition, both clinicians and patients may incorrectly attribute discontinuation symptoms to the underlying psychiatric illness for which the SRI was prescribed (i.e., a relapse) or to another psychiatric or medical condition. Currently, no evidence-based guidelines exist for active management of the SRI discontinuation syndrome. Such management strategies include slowing the rate of taper of the SRI and initiating an SRI with a longer half-life, such as fluoxetine. The purpose of this article is to describe the SRI discontinuation syndrome, to propose appropriate terminology and diagnostic criteria for this condition, and to discuss recognition, monitoring, and patient education. In addition, recent studies of the SRI discontinuation syndrome in neonates will be addressed.

PROPOSED TERMINOLOGY

There has been significant confusion regarding the nature of the SRI discontinuation syndrome due to inconsistent terminology. Unfortunately, the terms *discontinuation* and *withdrawal* have been used interchangeably, and the SRI discontinuation syndrome has been called *withdrawal* in scientific publications[7,9–18] as well as by the U.S. Food and Drug Administration.[19] However, while discontinuation technically means that the antidepressant has been withdrawn, the discontinuation syndrome is not synony-

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mous with a true *withdrawal* syndrome as that term is commonly used. SRI discontinuation syndrome is not analogous to other drug withdrawal conditions such as those associated with opiates or sedative-hypnotics (e.g., alcohol, barbiturates) in which hallmark symptoms include diaphoresis, tachycardia, tremor, myoclonus, anxiety, insomnia, seizures, and persistent drug craving.[20] In fact, the absence of drug craving may be the most distinguishing factor between discontinuation syndrome and withdrawal conditions. Individuals who discontinue SRIs typically do not consciously crave antidepressants, nor do they exhibit drug-seeking behavior. Symptoms following discontinuation of antidepressants are neither related to nor a result of a pattern of addiction. The term *withdrawal* may be particularly confusing to patients, many of whom are already concerned about becoming addicted to antidepressants. In fact, as many as 78% of people believe that antidepressants are addictive.[21] In contrast to withdrawal, discontinuation syndrome is unrelated to addiction, is more straightforward and manageable, and more conceptually similar to the physiologic responses following abrupt discontinuation of drugs for general medical conditions, such as insulin discontinuation in patients with diabetes.

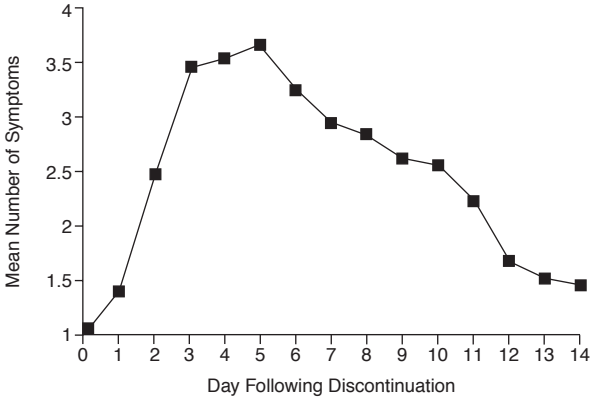
The term *discontinuation* is also often confused with *rebound* or *relapse*. While the SRI discontinuation syndrome is more analogous to the rebound effect seen following the discontinuation of insulin or antihypertensive agents than it is to withdrawal, it is somewhat more complex than a simple reemergence of disease symptoms. SRI discontinuation syndrome generally involves the return of some symptoms of the underlying disorder, such as anxiety and depressed mood, in addition to nondisease-related characteristics, such as flu-like symptoms and paresthesias.[1,2] In addition, discontinuation syndrome is time-limited—there is an acute emergence of symptoms that typically disappear within about 2 weeks (and generally do not persist beyond 3 weeks)—whereas relapse is associated with a longer—i.e., lasting for more than 3 weeks—persistence of symptoms.[2] Anything that is substantially present 3 weeks after discontinuation or dosage change is probably not related to the discontinuation syndrome and may be related either to a relapse or recurrence of the underlying disorder or to another intercurrent illness.

The recommendation is to avoid use of the term *withdrawal* in favor of *discontinuation syndrome*. This distinction is particularly relevant when communicating with patients, given the amount of misinformation in the popular media and the negative connotation associated with the term *withdrawal*.

HALLMARK FEATURES OF THE SRI DISCONTINUATION SYNDROME

As described by Schatzberg et al.,[2] the hallmark features of the SRI discontinuation syndrome are (1) not attributable to other causes; (2) emergent upon abrupt discontinuation of SRIs, intermittent nonadherence (e.g., missed doses, drug holidays), and, in some cases, dose reduction (although in the latter 2 cases symptoms are generally less frequent and usually less severe); (3) generally mild and short-lived (symptoms generally appear within 1 week after the drug is stopped or missed and usually disappear after about 2 weeks (Figure 1)[22]; (4) self-limiting (though they can be distressing); (5) rapidly reversed by the reintroduction of the original medication or the substitution of one that is pharmacologically similar; and (6) minimized by slow tapering or by adding a drug with an extended half-life, such as fluoxetine. The duration of the SRI discontinuation syndrome is consistent with the time frame for reregulation of receptors and transporters (2–14 days).[12]

Figure 1. Mean Number of Discontinuation Symptoms With Fluvoxamine[a]



[a]Reprinted with permission from Black et al.[22]

SYMPTOM CLUSTERS AND PROPOSED DIAGNOSTIC CRITERIA

Defining which symptoms constitute the SRI discontinuation syndrome can be challenging. In reviewing 46 case reports published between 1986 and 1997, Black et al.[23] identified 53 symptoms that were reported following the discontinuation of fluoxetine, fluvoxamine, paroxetine, or sertraline. The most commonly reported symptoms were dizziness, nausea, vomiting, fatigue, headache, gait disturbance (ataxia), paresthesias, shock-like sensations, and visual changes. These observations led the authors to propose the following diagnostic criteria for SRI discontinuation syndrome: (1) appearance within 1 to 7 days after discontinuation, (2) occurrence after ≥ 1 month of exposure, (3) duration of generally less than 3 weeks (from time of abrupt discontinuation or dose reduction), and (4) 2 or more of the symptoms listed in Table 1. Similar criteria have been reported by Haddad.[24] However, the majority of patients have additional symptoms, and each patient

Table 1. Proposed Diagnostic Criteria for SRI Discontinuation Syndrome[a]

Appearance within 1–7 days after discontinuation
Occurrence after ≥ 1 month of exposure
Duration of generally < 3 weeks after abrupt discontinuation or dose reduction
2 or more of the following symptoms:
Dizziness
Gait instability
Light-headedness
Headache
Vertigo/faintness
Insomnia
Paresthesias
Nausea or emesis
Anxiety
Tremor
Diarrhea
Visual disturbances
Fatigue

[a]Adapted with permission from Black et al.[23]
Abbreviation: SRI = serotonin reuptake inhibitor.

Table 2. Syndromic Features of SRI Discontinuation Syndrome

Syndromic Feature	Symptoms
Neurosensory	Vertigo
	Paresthesias
	Shock-like reactions
	Myalgias
	Other neuralgias
Neuromotor	Tremor
	Myoclonus
	Ataxia
	Visual changes
Gastrointestinal	Nausea
	Vomiting
	Diarrhea
	Anorexia
Neuropsychiatric	Anxiety
	Depressed mood
	Intensification of suicidal ideation
	Irritability
	Impulsiveness
Vasomotor	Diaphoresis
	Flushing
Other neurologic	Insomnia
	Vivid dreaming
	Asthenia/fatigue
	Chills

Abbreviation: SRI = serotonin reuptake inhibitor.

tends to have a unique set of discontinuation characteristics. Therefore, a more sophisticated diagnostic system, in which symptoms are grouped or clustered, may enable physicians to better recognize this phenomenon in their patients.

Schatzberg et al.[2] proposed 5 clusters of core somatic symptoms that are commonly observed in patients experiencing the SRI discontinuation syndrome. These include disequilibrium (e.g., dizziness, vertigo, ataxia); gastrointestinal symptoms (e.g., nausea, vomiting); flu-like symptoms (e.g., fatigue, lethargy, myalgia, chills); sensory disturbances (e.g., paresthesias, "electrical sensations"); and sleep disturbances (e.g., insomnia, vivid dreams). These symptom clusters have been confirmed in analyses of existing databases.[7,25]

An alternate method of categorizing symptoms of the SRI discontinuation syndrome would be according to the following syndromic features (Table 2): neurosensory (e.g., vertigo, paresthesias, shock-like reactions, myalgia, other neuralgia); neuromotor (e.g., tremor, myoclonus, ataxia, visual changes); gastrointestinal (e.g., nausea, vomiting, diarrhea, anorexia); neuropsychiatric (e.g., anxiety, depressed mood, intensification of suicidal ideation, irritability, impulsiveness); vasomotor (e.g., diaphoresis, flushing); and other neurologic (e.g., insomnia, vivid dreaming, asthenia/fatigue, chills). This classification system encompasses both somatic as well as psychological symptoms. These groups of symptoms tend to occur together—patients experiencing discontinuation often have 1 or 2 elements from each group.

PRACTICAL APPLICATION OF CRITERIA

Appropriate diagnostic criteria for the SRI discontinuation syndrome should allow clinicians to better diagnose this condition and to distinguish it from relapse after SRI discontinuation or dosage reduction. Specific guidelines for patient evaluation and management during SRI discontinuation are provided in the consensus recommendations article in this supplement.[26] However, a few recommended management strategies highlight the distinction between the SRI discontinuation syndrome and relapse and are worthy of additional discussion. Both the nature of the symptoms and the time course for the SRI discontinuation syndrome differentiate it from relapse. While relapse involves a return of symptoms from the index episode, patients experiencing discontinuation syndrome experience emotional symptoms plus symptoms from the other syndromic categories listed above. It may be best to wait until the symptoms have persisted for at least 3 weeks, if possible, to evaluate and assess management strategies if the discontinuation symptoms are mild and tolerable, as symptoms related to discontinuation will most likely resolve after 2 weeks. However, it is important that patients have clear directions in the event that they become very symptomatic: they should either contact their treating clinician or be given permission to restart the previous dose of medication on their own. If symptoms continue beyond 3 weeks, the patient has most likely relapsed and should probably restart the drug.

If the antidepressant dose is being gradually tapered, the 3-week rule applies to each step of the taper. In this situation, patients should be warned that the discontinuation effects may be more prolonged, since they may occur at each taper step. If the emotional symptoms associated with discontinuation, with or without tapering, are

extreme (e.g., acute depression, suicidal feelings), medical intervention, such as the introduction of a longer-acting selective serotonin reuptake inhibitor (e.g., fluoxetine), may be prudent.

In addition to managing patients who are undergoing supervised SRI discontinuation, clinicians should be aware that intermittent nonadherence or covert discontinuation of SRI treatment can elicit discontinuation symptoms. Published data indicate that 30% to 60% of patients do not take their medications as prescribed; therefore, nonadherence to antidepressant medication is likely to be a significant clinical issue in the management of many patients.[27] Thus, warning patients about the possibility of symptoms with missed doses is advised.

SRI DISCONTINUATION SYNDROME IN NEONATES

An SRI discontinuation–like syndrome has been observed in neonates exposed to maternal antidepressant use during pregnancy.[28,29] This possibility must be considered when treating pregnant women with antidepressants and should be discussed with all women of reproductive age. In a recent study,[30] there was a greater incidence of perinatal complications, including respiratory distress, hypoglycemia, and jaundice in infants exposed to paroxetine in the third trimester compared with those who were either never exposed or exposed prior to but not during the third trimester. Logistic regression demonstrated that only third trimester exposure was related to negative neonatal outcome. In an analysis of the World Health Organization database of adverse drug reactions, 64 of 93 cases of probable SRI-induced neonatal discontinuation syndrome were associated with paroxetine, 14 with fluoxetine, 9 with sertraline, and 7 with citalopram. There were 13 patients with seizures, 2 with hyponatremia, and 1 each with circulatory failure and coma. This suggests that more serious discontinuation effects can occur in the neonate, even though a causal relationship between the SRI discontinuation and these events cannot be established unequivocally.[31]

As noted, typical postnatal reactions, such as insomnia, irritability, and myoclonus, are suggestive of adult SRI discontinuation symptoms. However, other features, including respiratory distress, tonus, and seizures, seem unlike adult reactions. Recently, Haddad et al.[32] proposed that some reactions may be related to serotonin toxicity (serotonin syndrome). In addition, the residual drug in the blood of the neonate could produce a direct toxic effect. Still, the majority of these reactions are likely to be related to discontinuation effects, since they appear to occur at a higher frequency with short half-life antidepressants such as paroxetine.

Women taking SRIs who are of reproductive potential should be warned of the possibility for discontinuation syndrome in newborns so that they can manage this process if they become pregnant. For women planning to become pregnant who choose to continue treatment during pregnancy or those who have become pregnant while taking antidepressants, clinicians may consider a gradual switch to a longer-acting agent (e.g., sertraline, fluoxetine) before pregnancy or as early as possible in an established pregnancy. If the patient opts to discontinue treatment entirely, she should be informed that pregnant women may be particularly prone to relapsing, which may endanger the patient and/or the fetus, and evaluated for reinstitution of the antidepressant as soon as possible after delivery. Women who give birth while taking shorter-acting antidepressants should inform the clinician delivering the baby about the potential for discontinuation syndrome, and their infants should receive cautious management during the perinatal period. However, because the symptoms are not specific to discontinuation, it is important that neonates exhibiting signs or symptoms that may be attributable to discontinuation syndrome be given an appropriate workup to exclude other possible causes. Finally, it should be noted that GlaxoSmithKline, Inc., makers of branded Paxil, recently filed data with the U.S. Food and Drug Administration and changed their package labeling to indicate that paroxetine is associated with an increased frequency of birth defects after first trimester use and, therefore, should be avoided by pregnant women or those who could become pregnant.[33]

CONCLUSION

Antidepressant discontinuation syndrome is not rare, particularly following cessation of agents with shorter half-lives. Discontinuation symptoms are not related to either drug addiction or withdrawal, and the use of proper terminology when discussing this phenomenon with patients can help to alleviate concerns and prevent the perpetuation of commonly held misperceptions. Awareness of the unique nature of these effects and the typical time frame of their occurrence can assist in distinguishing between discontinuation syndrome and relapse. To prevent SRI discontinuation syndrome, clinicians should consider slow tapering and/or drug substitution when discontinuing treatment. Finally, it is imperative that both patients and significant others be provided with sufficient education and reassurance upon initiation of any antidepressant treatment.

Drug names: citalopram (Celexa and others), clomipramine (Anafranil and others), fluoxetine (Prozac and others), paroxetine (Paxil, Pexeva, and others), sertraline (Zoloft).

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