Serotonin Reuptake Inhibitor Discontinuation Syndrome: A Hypothetical Definition

Discontinuation Consensus Panel

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Adverse events following discontinuation from serotonin reuptake inhibitors (SRIs) are being reported in the literature with increasing frequency; the frequency and severity of these symptoms appear to vary according to the half-life of the SRI, e.g., the incidence appears higher with the shorter half-life agents than with fluoxetine, which has an extended half-life. Yet, there have been no systematic studies of the phenomenon to date. Therefore, a group of experts convened in Phoenix, Arizona, to develop a clear description or definition of the phenomenon based on these reports. The SRI discontinuation syndrome, referred to as "withdrawal symptoms" in many anecdotal case reports, is distinctly different from the classic withdrawal syndrome associated with alcohol and barbiturates. Antidepressants are not associated with dependence or drug-seeking behavior. SRI discontinuation symptoms tend to be short-lived and self-limiting, but can be troublesome. They may emerge when an SRI is abruptly discontinued, when doses are missed, and less frequently, during dosage reduction. In addition, the symptoms are not attributable to any other cause and can be reversed when the original agent is reinstituted, or one that is pharmacologically similar is substituted. SRI discontinuation symptoms, in most cases, may be minimized by slowly tapering antidepressant therapy, but there have been several case reports where symptoms occurred consistently even through repeated attempts to taper therapy. Physical symptoms include problems with balance, gastrointestinal and flu-like symptoms, and sensory and sleep disturbances. Psychological symptoms include anxiety and/or agitation, crying spells, and irritability. Further analyses of data bases and clinical studies are needed to define this proposed syndrome more clearly.

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When patients stop long-term therapy with antidepressants, mood stabilizers, or antipsychotics, discontinuation symptoms frequently occur. These symptoms range in severity from mild somatic distress and gastrointestinal symptoms, which sometimes appear upon tricyclic antidepressant (TCA) withdrawal, to serious cognitive impairment and catatonia that may lead to hospitalization, which can appear when monoamine oxidase inhibitors (MAOIs) are discontinued. However, even when severe, these symptoms are distinctly different from the classic withdrawal syndrome that is associated with sedative hypnotics such as alcohol and barbiturates. Many of the symptoms or symptom clusters that have been reported after discontinuation of the serotonin reuptake inhibitors (SRIs) are similar to those for tricyclic withdrawal, but a variety of novel symptoms are also associated with the stoppage of SRI therapy. Attempts to systematically study SRI discontinuation have been hampered by a lack of an operationalized definition. Thus, the purpose of this article is to create a hypothetical definition of an SRI discontinuation syndrome to facilitate research into a phenomenon that differs dramatically among the SRIs.

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WITHDRAWAL VS. DISCONTINUATION

Symptoms of antidepressant withdrawal have long been documented in the literature. Dilsaver et al.[1] reported

Table 1. Hallmark Features of Serotonin Reuptake Inhibitor Discontinuation Syndrome

Not attributable to other causes
Emergent upon abrupt discontinuation, intermittent noncompliance (e.g., missed doses, drug holidays), and, less frequently, with dose reduction
Generally mild and short-lived
Self-limiting but can be distressing
Rapidly reversed by the reintroduction of the original medication or the substitution of one that is pharmacologically similar
Minimized by slow tapering or by using a drug with an extended half-life

five symptom clusters that are associated with TCA discontinuation: general somatic distress, sleep disturbances, akathisia or parkinsonism, behavioral activation, and cardiac arrhythmias. These symptoms were all recorded in a group of seven patients; each subject was systematically evaluated for discontinuation phenomena by the same physician after TCA therapy was stopped abruptly.[2] Severe symptoms such as delirium have been described for MAOI discontinuation.[3] When treatment with serotonin selective reuptake inhibitors (SSRIs) is interrupted, symptoms are most likely to occur for paroxetine[4,5] and least likely for fluoxetine.[6,7] Withdrawal symptoms have also been reported for other antidepressants such as trazodone[8,9] and venlafaxine.[10,11] These symptoms are substantially different from rebound phenomena (such as insomnia or anxiety that return when medication is stopped), depressive relapse, or those associated with withdrawal from sedative hypnotics.

The features of withdrawal associated with sedative hypnotics such as alcohol and barbiturates range from sympathetic overdrive—diaphoresis, tachycardia, jitteriness—to convulsions, coma, cardiovascular collapse, and death. In addition, patients develop tolerance to these medications and display drug-seeking behavior. For example, obtaining alcohol becomes the overriding quest in an alcoholic's life—it eventually takes precedence over going to work and supporting a family. An alcoholic will continue to drink despite overt physical, psychological, and social harm. Physiology probably plays a role in the differences in these symptoms. Barbiturates—but not most antidepressants—have effects on the GABA (gamma-aminobutyric acid) neurotransmitter.

Unfortunately, the public often perceives wrongly that antidepressants—like alcohol and barbiturates—are addicting. In a recent survey of 2000 individuals, Priest et al.[12] found that 78% of those surveyed (N = 2003) thought that antidepressants are addictive and only 1 in 6 believed that depressed people should be offered antidepressant treatment. On the other hand, physicians, particularly those in general practice, are becoming more likely to prescribe antidepressants. Since 1993, the number of prescriptions written in Great Britain for the treatment of depression has increased by 33%, and the number written for SSRIs has risen by 134%,[13] but while more physicians are prescribing antidepressant treatment, few family care physicians and not all psychiatrists are aware that patients who discontinue treatment may experience new symptoms.[14]

HALLMARK FEATURES

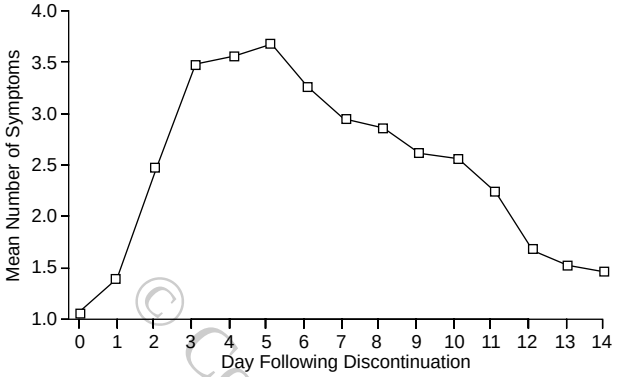
The incidence of discontinuation reactions after SRI cessation varies substantially in published reports. According to a postmarketing survey,[15] the incidence is extremely low (ranging from 0.06% to 5.1% of patients). On the other hand, anecdotal case reports of SRI discontinuation published in the literature have found rates of withdrawal symptomatology as high as 28% of fluvoxamine-treated patients[16] and 50% in a very small series of paroxetine-treated patients.[17] It appears that symptoms have been observed less frequently during abrupt discontinuation of fluoxetine.[6,18–20]

While defining a benzodiazepine withdrawal syndrome, Lader[21] suggested that the syndrome should have a well-defined and predictable onset, duration, and offset. The main characteristics of the proposed SRI discontinuation syndrome are that (1) it is not attributable to other causes; (2) it emerges after abrupt discontinuation, during periods of intermittent noncompliance (missed or forgotten doses), or less frequently, during dose reduction; (3) it is generally mild and transient, but can be troublesome and lead to missed work days and decreased productivity; (4) it is self-limiting; (5) it is rapidly reversed by the reintroduction of the original medication or the substitution of an agent that is pharmacologically similar; and (6) it may be minimized by slow tapering or the use of a drug with an extended half-life such as fluoxetine. (Table 1).

Emergence of New Symptoms

Symptoms of the SRI discontinuation syndrome should not be attributable to other causes. When new adverse events occurred in 5 of 13 subjects who were being tapered from paroxetine after a clinical trial for OCD, Keuthen et al.[22] noted that the symptoms "differed from side effects accompanying the medication trial." The authors further stated that the onset of the new symptoms paralleled the resolution of preexisting medication side effects. In another report,[23] the onset of new adverse effects came 3 days after a patient stopped taking paroxetine. The major side effect of the paroxetine treatment was hypomania, which resolved upon drug discontinuation; however, 3 days later, the patient began to experience anorexia, nausea, diarrhea, and shaking chills. Black et al.[24] noted that 14 subjects, who were assessed for symptoms of fluvoxamine discontinuation, were relatively asymptomatic at baseline when the drug was stopped and that symptoms occurring over the next 2 weeks differed from those at baseline.

Figure 1. Mean Number of Discontinuation Symptoms With Fluvoxamine*



*From reference 24 with permission.

Occurrence of Symptoms

In the vast majority of cases, SRI discontinuation symptoms commence within 1 to 3 days of termination, which is consistent with the half-lives of most SRIs, although symptoms have been reported during systematic tapering and following dosage reduction. Barr et al.[17] studied the effects of a 7- to 14-day paroxetine taper in six patients. Three developed a withdrawal syndrome despite the slow taper. The authors noted that symptoms of withdrawal may occur despite progressive dose reduction of paroxetine. Rauch et al.[11] reported that four of nine patients who were being treated with venlafaxine for obsessive-compulsive disorder (OCD) experienced troublesome symptoms when the dose was incrementally reduced over a period of time ranging from 4 days to 2 weeks. Three consecutive patients who experienced severe physical symptoms of withdrawal during venlafaxine discontinuation were reported by Gaikas and Davis.[25] Repeated attempts at gradually tapering the dosage were unsuccessful and led to intolerable withdrawal sensations. Symptoms occur less frequently and are usually milder in patients who take extended half-life agents such as fluoxetine, but when they occur, onset may be more than 1 week after the final dose. For example, one patient experienced mild dizziness and light-headedness 5 days after she stopped fluoxetine treatment for the first time and 9 days after a second discontinuation.[18]

Severity of Symptoms

While the SRI discontinuation syndrome is usually transient and mild, symptoms, at times, can become serious. Pacheco et al.[26] reported that two of five patients in whom symptomatology developed during paroxetine tapering needed acute treatment. Two other paroxetine-treated patients became manic for 9 to 17 days after treatment was stopped abruptly in one and tapered in the other.[27] After sertraline discontinuation, one patient felt electric shocks of such severity that he momentarily lost control of the steering wheel of his car.[28] Discontinuation symptoms sometimes lead to missed work. After fluvoxamine was abruptly discontinued, 5 of 14 patients who experienced symptoms (including dizziness/incoordination, headaches, irritability, and nausea) were absent from work for at least 1 day.[24]

Persistence of Symptoms

Symptoms of SRI discontinuation are usually short lived; most disappear within 2 weeks, but occasionally the symptoms last for several weeks. In the Black et al. study,[24] patients were evaluated for discontinuation events 5, 10 and 14 days after sudden fluvoxamine discontinuation. Symptoms were most frequently reported on Day 5 and few persisted on Day 14 (Figure 1). The authors of a retrospective chart review of 171 patients who were discontinued from an SRI found that symptoms persisted for a mean of 11.8 days after onset and a maximum of 21 days.[6]

Reversal of Symptoms

If the original antidepressant is reintroduced, or one that is pharmacologically similar is substituted for the original agent, the symptoms of discontinuation remit—usually within 24 hours. Symptoms resolved 1 day after fluoxetine treatment was reinstituted in an elderly woman who had become agitated and disoriented when the medication was temporarily discontinued because of hospitalization,[29] 1 to 2 days after 10 mg/day of paroxetine was restarted in 2 patients,[30] and within 24 hours in those patients who were restarted on their antidepressant in the retrospective chart review.[6] The discontinuation symptoms also remitted abruptly when fluoxetine was started in a patient who had been experiencing severe dizziness after paroxetine cessation.[22] In another patient, fluoxetine was used successfully to treat venlafaxine withdrawal symptoms.[25]

Minimizing the Syndrome

The discontinuation syndrome can be minimized by tapering the shorter acting SRIs extremely slowly or by selecting an antidepressant with an extended half-life such as fluoxetine. Slow taper may be particularly important for paroxetine, fluvoxamine, and venlafaxine, which have half-lives of 24 hours or less. The authors[26] of one report of paroxetine discontinuation symptoms in five young women in whom paroxetine was being tapered over a month noted that withdrawal symptomatology occurred despite conservative tapering and suggested that the paroxetine should be reduced by 5 mg/week—to below the minimum effective dose—to avoid a discontinuation syndrome. To reduce the risk of withdrawal symptoms, tapering of the shorter half-life SRIs fluvoxamine, paroxetine, and venlafaxine thus may have to continue for up to several weeks. Dominguez et al.[31] suggest that the extended half-life of fluoxetine and its active metabolite

Table 2. Core Somatic Symptoms

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., paresthesia, sensations of electric shock
Sleep disturbances, e.g., insomnia, vivid dreams

norfluoxetine protects patients against the emergence of discontinuation symptoms. This would be analogous to the relative lack of serious withdrawal reactions with the benzodiazepines such as chlordiazepoxide that have a long combined elimination half-life as compared with the shorter acting benzodiazepines such as lorazepam and alprazolam that do not have active metabolites.

CHARACTERISTIC SYMPTOMS

SRI discontinuation is characterized by a cluster of somatic and psychological symptoms. Some are similar to the phenomena that have been described by Dilsaver et al.[1] during TCA withdrawal, and some are unique to the SRIs. The manifestation of these symptoms in individual patients often depends on the rate of taper and the half-life of the agent being stopped. None or only a few symptoms might appear in patients who gradually taper the SRI or who are taking a medication with an extended half-life, while a cluster of symptoms is frequent in patients who suddenly stop taking a short half-life SRI.

Most of the symptoms associated with SRI withdrawal are physical rather than psychological. Five clusters of somatic symptoms have been reported frequently in the literature (Table 2): (1) disequilibrium (e.g., dizziness, vertigo, ataxia), (2) gastrointestinal symptoms (e.g., nausea, vomiting), (3) flu-like symptoms (e.g., fatigue, lethargy, myalgia, chills), (4) sensory disturbances (e.g., paresthesia, sensations of electric shock), and (5) sleep disturbances (e.g., insomnia, vivid dreams).

The incidence of these symptom clusters have been confirmed by two analyses of existing data bases on discontinuation reactions. Coupland et al.[6] conducted a retrospective chart review of 352 outpatients who were treated with one of the SRIs. In the 171 patients who were supervised during drug discontinuation, the most common somatic symptoms were dizziness, paresthesia, lethargy, and nausea, but vivid dreams, insomnia, headache, and movement-related symptoms were also reported (Table 3). Similarly, in an analysis of the United Kingdom data base of 271 spontaneously reported discontinuation reactions,[15] somatic symptoms were varied and included dizziness, paresthesia, tremor, nausea, and palpitations. Additionally, Lane[32] noted in a review of the literature on discontinuation that dizziness, sweating, nausea, insomnia, tremor, and headache have all been reported after SRI therapy is stopped.

A number of descriptors have been communicated by patients to describe the physical symptoms associated with SRI discontinuation. Dizziness has been reported as having a "swimming," "spaced out," "drunken," or "buzzing" quality and is often exacerbated by slight movements.[6] Sensory disturbances, which include a feeling of "burning," "tingling," or "electric shocks" have been described. These tend to be localized mainly to the upper half of the body and the face, and they are intense and distracting sensations that usually last a few seconds. Lethargy is occasionally a new symptom of sudden onset and at other times, a worsening of a previous symptom. Sleep disturbances included initial or middle insomnia and vivid or abnormal dreams. Instead of being in black and white, the dreams are often in color and contain frightening images of either self-harm or harm to a loved one. Insomnia, in some cases, represented onset of a symptom that had disappeared previously when the patient responded to antidepressant treatment.

As well as the somatic symptoms, several core psychological symptoms—anxiety/agitation, crying spells, and irritability—are associated with SRI discontinuation (Table 4). Anxiety/agitation was listed as frequent in the Coupland et al.,[6] Price et al.,[15] and Lane[32] reports, and Coupland et al. and Lane both described irritability as a common symptom. The crying spells, in particular, are dramatic and disappear quickly when the SRI is reintroduced.[31]

A number of other psychological phenomena are also noted in the literature about SRI discontinuation phenomena, but cannot be considered as core symptoms of SRI discontinuation. They include overactivity, depersonalization, lowered mood, memory problems, confusion, and decreased concentration and/or slowed thinking.

RISK FACTORS

Use of an antidepressant with a short half-life may be an important risk factor for SRI discontinuation events. The majority of reports of discontinuation reactions drawn from national data bases of spontaneously reported events[4,5,15] involve paroxetine, which has a half-life of 21 hours as compared with over 3 days for fluoxetine, the SRI with the longest half-life and the one involved in the fewest reports of discontinuation reactions. However, one cannot rule out the effects of differences in when specific agents were introduced into the market on reporting of incidents. Still, Coupland et al.[6] found that patients discontinuing the shorter half-life SSRIs, paroxetine and fluvoxamine, were significantly more likely to experience dizziness, paresthesia, lethargy, nausea, and movement-related symptoms than those discontinuing sertraline and fluoxetine. Frost and Lal[28] proposed that the extended half-life of fluoxetine may account for why patients are less likely to experience symptoms when fluoxetine treatment is stopped.

Table 3. Frequency (%) of Specific Somatic Symptoms During SRI Withdrawal*

	Clomipramine (N = 13)		Paroxetine (N = 59)		Fluvoxamine (N = 43)		Sertraline (N = 45)		Fluoxetine (N = 20)
Symptom	N	%	N	%	N	%	N	%	%
Dizziness	2	7.7	8	16.0	4	9.3	1	2.2	0.0
Paresthesia	4	30.8	6	12.0	1	2.3	0	0.0	0.0
Lethargy	1	7.7	6	12.0	2	4.7	0	0.0	0.0
Nausea	2	15.4	3	6.0	3	7.0	0	0.0	0.0
Vivid dreams	2	15.4	2	4.0	3	7.0	0	0.0	0.0
Insomnia	2	15.4	2	4.0	1	2.3	0	0.0	0.0
Headache	0	0.0	0	0.0	3	7.0	0	0.0	0.0
Movement-related	0	0.0	8	16.0	3	7.0	0	0.0	0.0

*Adapted from reference 6. Abbreviation SRI = Serotonin reuptake inhibitor.

Table 4. Psychological Symptoms

Core
Anxiety/agitation
Crying spells
Irritability
Also reported
Overactivity
Depersonalization
Decreased concentration/slowed thinking
Lowered mood
Confusion
Memory Problems

Length of antidepressant treatment is another factor that may affect risk. Coupland et al.[6] noted that symptoms occurred significantly more frequently in patients who had been taking antidepressants for 2 months or more than in those whose treatment was of a shorter duration. Fava and Grandi[7] also reported that withdrawal syndromes tend to occur only after 3 to 4 months of paroxetine treatment. Clinical experience indicates that patients who have had discontinuation symptoms once are likely to do so again and that the phenomenon is more likely to occur in patients with a history of noncompliance to antidepressant medication. Finally, patients who show treatment-emergent anxiety symptoms may be more likely to have symptoms upon SRI discontinuation.

CONCLUSION

The frequency of reports of symptoms that occur during SRI discontinuation is increasing. Thus, a definition or description of the "syndrome" has been proposed. The syndrome may emerge when SRIs are discontinued suddenly, when doses are missed or forgotten, or, occasionally, when doses are lowered. It is not attributable to other causes, is generally mild and short-lived, and is self-limiting, but it can be distressing. Withdrawal symptoms are rapidly reversed by the reintroduction of the original medication or one that is pharmacologically similar and can be minimized by slow tapering or by using a drug with an extended half-life. Physical symptoms include problems with balance; nausea and vomiting; fatigue, lethargy, myalgia, and chills that feel like the flu; and sensory and sleep disturbances. Psychological symptoms include anxiety, irritability, and crying spells.

Controlled studies of SRI discontinuation in large numbers of patients are needed and are underway to test this hypothetical definition and to answer several further research questions such as:

- Does the discontinuation syndrome vary in prevalence or in form among the SRIs?
- Do the number of symptoms and the severity differ in patients with specific disorders?
- Does the antidepressant dose correlate with the risk of the discontinuation syndrome?

Drug names: alprazolam (Xanax), chlordiazepoxide (Librium and others), fluoxetine (Prozac), fluvoxamine (Luvox), lorazepam (Ativan and others), paroxetine (Paxil), sertraline (Zoloft), trazodone (Desyrel and others), venlafaxine (Effexor)

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Discussion

Dr. Zajecka: A syndrome is a cluster of symptoms. We've identified a cluster of symptoms that appear on discontinuation and sometimes even after lowering the dose. I think this cluster of symptoms can be defined as a discontinuation syndrome.

Dr. Rosenbaum: Our hypothesis will soon be able to be tested in extant data bases. One of these data bases is already compiled, and an analysis of discontinuation reactions in 50 patients who stopped SSRI treatment is being prepared. In another study now under way, patients are being discontinued from treatment early and late in the course of treatment. This double-blind study is being conducted at several centers.

Dr. Haddad: In your research, have you seen that this syndrome has diverse manifestations?

Dr. Rosenbaum: Yes, and there are still many open questions. Is the syndrome subtly different for different agents? For different subtypes of patients? For different doses and durations of treatment?

Dr. Zajecka: We need to establish a definition of a sensory disturbance. The literature discusses both paresthesias and electrical sensations.

Our purpose is to encourage clinicians to think about the possibility of discontinuation symptoms and to not misdiagnose patients who come in to report fatigue as having a recurrence of depression. Lethargy, headache, myalgias, and chills are all commonly reported symptoms, and clinicians are likely to understand the term "flu-like."

Dr. Rosenbaum: If clinicians remember disequilibrium, gastrointestinal and flu-like symptoms, and sleep and sensory disturbances, they will have a good picture of the discontinuation syndrome, according to our proposed definition.

Dr. Schatzberg: The existing studies are nonprospective and lack a baseline list of symptoms for researchers to use to discover whether a patient who is experiencing excitement on discontinuation is a person who was excited before starting treatment.

Dr. Kaplan: We have not discussed discontinuation symptoms associated with venlafaxine sufficiently, because data on this phenomenon are lacking. However, in clinical practice, we are frequently seeing discontinuation symptoms associated with a reduction in the dose of venlafaxine.

Dr. Zajecka: Most analyses of reported discontinuation phenomena fail to include venlafaxine, although I have seen patients with discontinuation symptoms 12 hours after they miss a venlafaxine dose.

Dr. Rosenbaum: Discontinuation events occur dramatically and commonly when the venlafaxine dose is adjusted downward as well as on discontinuation.

Mauricio Fava, M.D., and I conducted a prospective study of antidepressant discontinuation at the Massachusetts General Hospital. The symptoms that emerged during venlafaxine discontinuation were dizziness, hot and cold flashes, excessive sweating, nausea, unsteady gait, headache, irritability, dysphoria, and insomnia—the same symptoms that keep appearing after SSRI discontinuation.

Dr. Zajecka: The prescribing information for venlafaxine recommends that, to minimize the risk of discontinuation symptoms, the medication be tapered if patients have been taking it for more than 1 week.