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Selective Serotonin Reuptake Inhibitor Discontinuation Syndrome: A Review

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ABSTRACT

Selective serotonin reuptake inhibitors (SSRIs) are widely prescribed in the treatment of depression and anxiety, as well as obsessive-compulsive, eating, and impulse-control disorders. Paralleling their widespread use has been an increase in adverse-effect reports not noted during short-term efficacy studies. Significant among these adverse effects is SSRI discontinuation syndrome, which follows the interruption of extended treatment or a reduction in drug dosage and entails somatic and psychological symptoms. These self-limiting symptoms resolve on reintroduction of the drug and cannot be explained as a remanifestation of the original disorder. To facilitate proper diagnosis and avoid unnecessary therapeutic or diagnostic interventions, all physicians who prescribe SSRIs should become familiar with these symptoms. The most appropriate approach to therapy for discontinuation syndrome involves educating patients and reassuring them that this is a reversible condition, reinstating the original SSRI, and further slowing the rate of tapering.

Keywords: selective serotonin reuptake inhibitors; antidepressants; discontinuation syndrome; adverse effects

INTRODUCTION

Selective serotonin reuptake inhibitors (SSRIs) have been used effectively in the treatment of mood, anxiety, eating, and impulse-control disorders for the past 10 years.[1] Recent studies have revealed the necessity of long-term therapy with these drugs for several conditions.[2] Paralleling the widespread extended use of SSRIs were reports of several side effects that were not determined or observed during short-term drug efficacy trials. One

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such entity is SSRI discontinuation syndrome, which has drawn significant research interest in recent years.[3-13] Appearing at first in case reports,[14-25] this phenomenon has now been documented in an impressive number of controlled studies.[3,4,6,7,12,26,27]

Discontinuation syndrome comprises several characteristic signs and symptoms that follow the cessation or dose reduction of a drug.[28] These symptoms are generally self-limiting, resolve rapidly after recommencement of the drug, and cannot be explained by a recurrence of the disorder being treated. Antidepressant-related discontinuation symptoms were first reported for imipramine in 1959 and have since been identified with other tricyclic antidepressants (TCAs) and monoamine oxidase (MAO) inhibitors.[29] The initial SSRI discontinuation syndrome was described for fluoxetine in 1988.[30] Subsequent case reports and large studies documented its occurrence with all other SSRIs, primarily paroxetine,[6,7,27] as well as with psychotropic agents affecting the serotonergic system, such as venlafaxine,[15] nefazodone,[21] and mirtazapine.[14]

This paper reviews the epidemiology, clinical features, etiology, treatment, and compensation strategies of SSRI discontinuation syndrome.

INCIDENCE AND PREVALENCE

Although a class effect of SSRIs, discontinuation syndrome occurs most frequently with paroxetine (Table 1).[12,26] A recent meta-analysis[6] of all case reports and research published up to 1997 found that 30 of 46 cases (65%) were linked to paroxetine, compared with 8 (17%) for sertraline, 5 (11%) for fluoxetine, and 3 (7%) for fluvoxamine. The frequency of the syndrome ranged from 7.2% with SSRIs with a short half-life (paroxetine and fluvoxamine) to as low as 2.2% with SSRIs with a longer half-life (sertraline and fluoxetine).[26] Withdrawal reactions were 10 times more frequent with paroxetine than with sertraline and fluvoxamine and 100 times more frequent than with fluoxetine. In a controlled study of 220 patients,[11] the incidence of an SSRI discontinuation syndrome observed in fluoxetine-treated patients (14%) was significantly lower than the pooled incidence for sertraline- (60%) and paroxetine-treated (66%) patients. Studies of citalopram were scarce in the literature because of the drug's relatively late availability in the US market; however, no clear-cut discontinuation syndrome was observed in a small prospective pilot study of citalopram in 4 patients.[31] Another study[14] reported that withdrawal of citalopram had a low likelihood of causing a discontinuation syndrome. Overall assessment of these various incidence figures shows the highest rates of discontinuation syndrome with paroxetine withdrawal, the lowest with fluoxetine; this finding is consistent with most studies in this field. The high rate with paroxetine in one discussion,[1] however (peak figure was 55% in that paper), is comparable to that reported for several TCAs and MAO inhibitors.

In contrast to high rates—up to 100%—reported in studies that specifically assessed SSRI discontinuation symptoms, clinical trial databases held by several pharmaceutical companies report few patients with these symptoms.[1,8] The discrepancy may be explained by the paucity of clinical trials specifically designed to investigate this phenomenon.[1] Other reasons for the disparate results are the absence of a discontinuation phase in many trials; the failure of many drug trials to continue antidepressant treatment beyond 6 to 8 weeks, thereby limiting the likely occurrence

of discontinuation symptoms after this period; the failure of patients to report the relatively mild clinical symptoms caused by discontinuation; and the spontaneous recovery within 3 to 5 days.

Table 1. Generic and Trade Names of Medications Associated With SSRI Discontinuation Syndrome

Generic Name	Trade Name*	How Supplied
Citalopram hydrobromide	Celexa™	20-, 40-mg tablets
Fluvoxamine maleate	Luvox®	25-, 50-, 100-mg tablets
Paroxetine hydrochloride	Paxil®	10-, 20-, 30-, 40-mg tablets Oral suspension (10 mg/5 mL)
Fluoxetine hydrochloride	Prozac®	10-, 20-, 40-mg Pulvules® 10-mg tablet
Sertraline hydrochloride	Zoloft®	25-, 50-, 100-mg tablets Oral concentrate (20 mg/mL)
Venlafaxine hydrochloride	Effexor®	25-, 37.5-, 50-, 75-, 100-mg tablets
	Effexor® XR	37.5- 75-, 150-mg extended-release capsules
Nefazodone hydrochloride	Serzone®	100-, 150-, 200-, 250-mg tablets
Mirtazapine	Remeron®	15-, 30-, 45-mg tablets

*Within the United States.

Celexa is a trademark of Forest Pharmaceuticals, Inc, St. Louis, Mo; Luvox is a registered trademark of Solvay Pharmaceuticals, Inc, Marietta, Ga; Paxil is a registered trademark of GlaxoSmithKline, Research Triangle Park, NC; Prozac is a registered trademark of Eli Lilly and Company, Indianapolis, Ind; Zoloft is a registered trademark of Pfizer Inc., New York, NY; Effexor and Effexor XR are registered trademarks of Wyeth-Ayerst Pharmaceuticals, Philadelphia, Pa; Serzone is a registered trademark of Bristol-Myers Squibb, Princeton, NJ; Remeron is a registered trademark of Organon Inc, West Orange, NJ.

CLINICAL SYMPTOMS

Various studies have described SSRI discontinuation syndromes consisting of 10 to 53 physical or psychological symptoms.[1,3,5,6,26] The most common symptoms were dizziness, nausea/vomiting, headache, and lethargy.[6,26]

Over the past three decades, discontinuation syndromes also have been frequently reported with TCAs and MAO inhibitors.[8] Symptoms of discontinuation from MAO inhibitors are generally more severe than those from SSRIs, with characteristic cognitive impairments and delirium. Also noted were psychosis, depression, thought disorders, mania, hypomania, agitation, aggressiveness, insomnia, and myoclonic jerks.[9]

TCA discontinuation symptoms have been classified into five main groups[32]: (1) gastrointestinal and general somatic distress symptoms, eg, anxiety, agitation, muscle tension, nervousness, flu-like symptoms (fatigue, headache, sweating, myalgia), lethargy, nausea, vomiting, asthenia; (2) sleep disturbances, such as insomnia and excessive and vivid dreams; (3) movement disorders, eg, akathisia, parkinsonism, unsteady gait, abnormal movements of mouth and tongue; (4) behavioral activation, such as panic attacks, delirium, mania or hypomania; and (5) miscellaneous symptoms, such as cardiac arrhythmias. SSRI discontinuation syndrome includes these groups except for cardiac arrhythmias.[1] Three additional symptom clusters that follow SSRI termination which are not included in the TCA classification are (1) problems with balance (dizziness, ataxia, vertigo); (2) sensory abnormalities (electric shock–like sensations, paresthesia); and (3) aggressive and impulsive behavior (suicide attempts, hoarding during discontinuation).

CLINICAL COURSE

In the vast majority of patients, SSRI discontinuation symptoms occur within 1 to 3 days after cessation of treatment or reduction in dose.[28] Of 42 patients in one study,[6] 81.3% had onset of withdrawal symptoms within 1 to 3 days and 93.8% within 1 week; all patients were symptomatic within 2 weeks. In another study,[4] a median of 2.1 days elapsed between cessation of treatment with paroxetine and onset of symptoms. Discontinuation symptoms with fluvoxamine reached their maximum on the fifth day after the last dose.[5]

In most cases, the discontinuation syndrome is mild and short-lived, even if untreated.[9,26] In a retrospective chart review of 171 patients,[26] symptoms persisted for a mean of 11.8 days after onset, with a maximum of 3 weeks, independent of the type of SSRI. In a recent meta-analysis[6] of 26 cases of spontaneous resolution, 47.6% of symptoms resolved in less than 1 week; in the remainder of the cases, symptoms lasted longer. One patient experienced a discontinuation syndrome lasting 13 weeks.[18] Five patients (3 taking paroxetine, 1 each taking fluoxetine and citalopram), between 29 and 49 years of age, all suffered prolonged neurologic symptoms (nocturnal twitching, irritability, paresthesia, myoclonic jerks) for as long as 18 months after discontinuing their medication.[19] These cases of prolonged SSRI discontinuation syndromes are unique in the literature.

CLINICAL FEATURES

SSRI discontinuation syndromes usually appear after at least 4 weeks of treatment.[33] In a study of 171 patients,[26] the syndrome did not occur when treatment lasted fewer than 7 weeks. In addition, extending SSRI exposure beyond 6 months did not seem to increase the risk of the syndrome. These findings support the hypothesis that a minimum period is required to establish new physiologic conditions related to drug administration but that drug-related changes are stable at once.[27]

Despite a few reports to the contrary,[3,4] most research has concluded that neither age nor sex appears to influence the incidence rate or nature of discontinuation symptoms.[1,26,27] Indeed, the syndrome has been observed among neonates,[34-36] children, and adolescents.[16] Discontinuation symptoms in newborns included agitation, restlessness, poor feeding and sleep patterns, constant crying, and enhanced startle reaction.[35,36] Mild and transitory postnatal complications (jitteriness, irritability, sleep disturbances) were observed in 13% of 115 infants whose mothers had taken fluoxetine in the third trimester of pregnancy.[34] A 9-year-old boy experienced withdrawal symptoms associated with abrupt paroxetine discontinuation.[16] Compared with that in adults, the higher rate of drug metabolism in children may make them more vulnerable to withdrawal symptoms within a short time after abrupt tapering of paroxetine.

PATHOGENESIS

The mechanisms underlying SSRI discontinuation syndrome are not clearly defined, but several possibilities have been proposed,[1,10-12] including four main hypotheses[37]: a decrease in available serotonin, secondary effects on other neurotransmitters, individual differences in patients, and cholinergic rebound.

The simplest explanation is a decreased level of serotonin in synapses and synaptic vesicles. This deficiency takes different clinical forms depending on the type of SSRI.[33,37] There appears to be a meaningful relationship between the plasma half-lives of SSRIs (fluoxetine, 2–6 days; paroxetine, 10–21 hours; sertraline, 26 hours; citalopram, 33 hours; fluvoxamine, 15–22 hours) and the occurrence of discontinuation syndrome on abrupt discontinuation or interruption of treatment.[2,27] The syndrome is most common with paroxetine, which has the shortest half-life and no active metabolites, and relatively uncommon with fluoxetine, which has the longest half-life of SSRIs and an active metabolite, norfluoxetine, that further extends this half-life from 7 to 17 days.[11] Although the half-life of sertraline is similar to that of paroxetine, an active metabolite (desmethylsertraline, with a half-life of 62 to 104 hours) may explain its lower propensity to cause discontinuation syndrome.[1] Many studies have demonstrated a pattern of symptom emergence and increased severity that parallels the drugs' plasma half-lives, strongly suggesting that half-life is most important to the occurrence of discontinuation syndrome.[1,26,27,33,37]

Another possible pathogenetic factor is an autoinhibition feature of some SSRIs.[1] Both paroxetine and fluoxetine are metabolized by cytochrome P450 2D6 enzymes and inhibit their own metabolism.[2] This results in nonlinear kinetics and disproportionate declines in plasma concentrations during drug discontinuation.[28] The short half-life and marked autoinhibition of paroxetine accelerate the decline of plasma levels that predisposes to rapid appearance of discontinuation syndrome. Despite marked autoinhibition properties, however, the long half-life and active metabolite of fluoxetine prevent significant occurrence of SSRI discontinuation syndrome.[1]

Another serotonergic hypothesis suggested that the reuptake blockade of serotonin will result over time in the down-regulation (desensitization) of postsynaptic serotonin receptors.[12] Reversal of serotonin reuptake blockade may restore possible acute enhancement of serotonin reuptake activity on discontinuation of SSRI and acutely deplete synaptic serotonin. These changes could be closely associated with discontinuation symptoms.[10]

A hyposerotonergic state due to withdrawal of SSRIs is proposed to have direct or indirect effects on other neurotransmitter systems such as acetylcholine, gamma-aminobutyric acid, norepinephrine, and dopamine, resulting in a variety of clinical symptoms.[12] Readaptation of these neurotransmitter systems takes about 2 to 3 weeks, which correlates with spontaneous alleviation of discontinuation symptoms.

Individual genetic or psychological differences are also accepted as contributing to SSRI discontinuation syndrome.[25,37] For example, 15% of the population lacks a serotonin transporter gene; therefore, the perturbing effects of treatment and its discontinuation are likely to be different for these individuals.[37] Genetic polymorphisms within the cytochrome P450 enzyme system may also be responsible for individual differences, as the 2D6 isoenzyme is involved in the metabolism of citalopram, fluoxetine, and paroxetine. Psychological characteristics like cognitive status may influence how patients perceive the severity of discontinuation symptoms and whether they decide to report the symptoms to their doctors.[1]

Cholinergic rebound is believed to be a major contributor to TCA discontinuation syndrome[8,9] and may account for the relatively frequent occurrence of SSRI discontinuation syndrome with paroxetine, which has the highest affinity for cholinergic receptors (approximately the same as TCAs).[9] Nevertheless, in two patients, desipramine (a TCA with muscarinergic-receptor affinity similar to that of paroxetine) could not reverse discontinuation symptoms associated with paroxetine, thus calling into question the cholinergic-rebound theory as the sole explanation for the SSRI discontinuation syndrome.[17]

DIAGNOSIS AND CLINICAL IMPLICATIONS

When initiating antidepressant therapy with an SSRI, a physician must consider the risk of discontinuation syndrome during or at the termination of treatment[38-40] and thus avoid failing to recognize symptoms.

Missing even a dose of an SSRI might lead to discontinuation syndrome.[39] As many patients do not report a missed dose unless they are persistently and directly questioned, anxiety, irritability, fatigue, and insomnia may be interpreted as depressive symptoms and mistaken for a relapse of the depressive episode. This, in turn, may lead to recommencement of a discontinued treatment, an increase in dosage,

a change in drug, or addition of a new drug. Moreover, because this syndrome involves mainly physical symptoms, patients may be subjected to costly and unnecessary diagnostic tests. Recognition of the link between discontinuation symptoms and drug cessation may make patients reluctant to use antidepressants and bolster their misbelief that all psychotropics are addictive.[39]

On the basis of literature findings, diagnostic criteria for SSRI discontinuation syndrome have been proposed in two articles (Table 2).

Table 2. Proposed Diagnostic Criteria for SSRI Discontinuation Syndrome

A. Discontinuation of or reduction in dose of an SSRI after at least 1 month of use

B. Two or more of the following symptoms appear within 1 to 10 days of Criterion A (within 1 to 7 days according to Black et al)

(Haddad, 1998)[1]	**(Black et al, 2000)**[6]
1. Dizziness or lightheadedness	**1.** Dizziness, lightheadedness, vertigo, or feeling faint
2. Nausea or vomiting	**2.** Nausea and/or emesis
3. Headaches	**3.** Headache
4. Lethargy	**4.** Visual disturbances
5. Anxiety or agitation	**5.** Anxiety
6. Tingling (ie, paresthesia), numbness, or electric shock–like sensations	**6.** Shock-like sensations or paresthesia
7. Tremor	**7.** Tremor
8. Sweating	**8.** Fatigue
9. Insomnia	**9.** Insomnia
10. Irritability	**10.** Irritability
11. Vertigo	**11.** Gait instability
12. Diarrhea	**12.** Diarrhea

C. Criterion B symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning

D. The symptoms are not due to a general medical condition and are not better accounted for by recurrence of the mental disorder for which an SSRI was originally prescribed, or by concurrent discontinuation (or reduction in use) of another psychoactive substance*

*Criterion D is included in Haddad's criteria as two separate items

TREATMENT AND PREVENTION

Several strategies have been suggested to manage discontinuation symptoms associated with SSRIs.[38] First, patients should be told that the symptoms are likely to be short-lived and mild; at this point, patients need only reassurance. An educational intervention conveying appropriate messages may help them cope with these side effects.[39] Compliance with therapy then plays a major role. Patients should consistently be reminded of the importance of taking their medication regularly, as even intermittent noncompliance (missing a single dose of SSRIs with short half-lives) can lead to discontinuation symptoms. Specific points addressed to patients may include[39]: (1) it will take 2 to 4 weeks before you notice beneficial effects; (2) you should continue taking the medication even after you begin to feel better; (3) check with your physician before you stop taking the antidepressants; (4) take the medication as directed; and (5) call your physician with questions.

When treatment has been successfully completed, all SSRIs, excluding fluoxetine, venlafaxine, nefazodone, mirtazapine, and other serotonergic drugs, should be tapered slowly to the minimum therapeutic dose and then terminated. Often, the final dose of many SSRIs must be lower than the starting dose.[38]

The rate of tapering should depend on the drug's pharmacologic profile, current dose, and duration of treatment.[8,12] Because of its increased potential for discontinuation syndrome, paroxetine should be tapered with special slowness and the rate estimated according to the patient's compliance, clinical status, and severity of possible symptoms.[39] Sometimes, despite slow tapering, symptoms may still emerge, whereupon the original dose must be reinstated and tapering extended for weeks, if necessary.[41] As reports about the effectiveness of starting a different SSRI at this phase are contradictory, the original SSRI should be reinstated until further evidence accumulates.[1] If side effects or severe discontinuation symptoms render continuing the original drug untenable, substituting fluoxetine, which has an extended half-life, for other SSRIs is an option. During treatment of discontinuation syndrome, reinstatement of SSRIs usually leads to resolution of symptoms within 24 to 48 hours.

In addition to these strategies, several case reports suggest that diphenhydramine (for muscle spasms, extrapyramidal symptoms), benzodiazepines (for insomnia and anxiety), ondansetron (for nausea, vomiting, diarrhea, and headache), and ginkgo biloba extract (for vertigo, dizziness) be used for discontinuation symptoms.[1,23,42]

CONCLUSIONS

All SSRIs, a first-line treatment option in many psychiatric disorders, can produce discontinuation syndrome after abrupt cessation of the drug or during reduction of the dose before termination. To facilitate proper diagnosis and avoid unnecessary therapeutic or diagnostic interventions, physicians who prescribe SSRIs should become familiar with these symptoms. The most appropriate approach to therapy for discontinuation syndrome entails educating patients and reassuring them that this is a reversible condition, reinstating the original SSRI, and further slowing the rate of tapering.

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