Selective serotonin reuptake inhibitor discontinuation syndrome: proposed diagnostic criteria

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Objective: To establish specific criteria by which selective serotonin reuptake inhibitor (SSRI) discontinuation syndrome may be identified. **Data sources:** MEDLINE and PSYCHLIT databases were searched for case reports published from 1986 to 1997 inclusive, and references of relevant articles were also searched. **Study selection:** Forty-six case reports of symptoms following the discontinuation of fluoxetine, fluvoxamine, paroxetine or sertraline were selected. Three studies of SSRI discontinuation were also reviewed. **Data extraction:** Demographic and treatment information, as well as the timing, duration, number, nature and frequency of dicontinuation symptoms. **Data synthesis:** Paroxetine was most frequently implicated. The drug had been tapered in half of the cases. In some cases, symptom onset began during taper, whereas, in most cases, symptoms began within 1 to 3 days of drug discontinuation. Fifty-three different symptoms were reported, with dizziness being the most common. Other common symptoms were nausea or emesis, fatigue, headache, gait instability and insomnia. Shock-like sensations, paresthesia and visual disturbances were the most rare. Without intervention, symptoms persisted for more than a week in half of the cases. In cases in which the SSRI was restarted, symptoms resolved within 72 hours. In some cases, withdrawal symptoms recurred when the same SSRI was again discontinued. **Conclusions:** Findings were used to construct diagnostic criteria for the SSRI discontinuation syndrome. These criteria are 2 or more of the following symptoms developing within 1 to 7 days of discontinuation or reduction in dosage of an SSRI after at least 1 month's use, when these symptoms cause clinically significant distress or impairment and are not due to a general medical condition or recurrence of a mental disorder: dizziness, light-headedness, vertigo or feeling faint; shock-like sensations or paresthesia; anxiety; diarrhea; fatigue; gait instability; headache; insomnia; irritability; nausea or emesis; tremor; and visual disturbances.

Objectif : Établir des critères spécifiques permettant de diagnostiquer le syndrome d'interruption du traitement à l'inhibiteur sélectif du recaptage de la sérotonine (ISRS). **Sources de données :** On a effec-

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Medical subject headings: antidepressive agents; fluoxetine; fluvoxamine; paroxetine; serotonin uptake inhibitors; sertraline; substance withdrawal syndrome

J Psychiatry Neurosci 2000;25(3):255-61.

Submitted May 19, 1999
Revised Oct. 7, 1999
Accepted Dec. 1, 1999

tué des recherches dans les bases de données MEDLINE et PSYCHLIT pour y trouver des rapports de cas publiés de 1986 à 1997 inclusivement, et on a aussi cherché dans les références des articles pertinents. **Sélection des études :** On a choisi 46 rapports de cas décrivant des symptômes se manifestant après l'interruption du traitement à la fluoxétine, à la fluvoxamine, à la paroxétine ou à la sertraline. On a aussi passé en revue trois études portant sur l'interruption du traitement à l'ISRS. **Extraction des données :** Information sur la démographie et le traitement ainsi que moment, durée, nombre, nature et fréquence des symptômes de l'interruption. **Synthèse des données :** La paroxétine était le médicament le plus souvent en cause. On en avait réduit graduellement l'absorption dans la moitié des cas. Dans certains cas, les symptômes ont fait leur apparition au cours de la réduction graduelle, tandis que dans la plupart des cas, ils ont commencé à se manifester un à trois jours après l'interruption du traitement au médicament. On a signalé 53 symptômes différents, les étourdissements étant les plus fréquents. Les nausées ou les vomissements, la fatigue, les maux de tête, l'instabilité de la démarche et l'insomnie étaient d'autres symptômes fréquents. Les sensations ressemblant à l'état de choc, la paresthésie et les troubles de la vue étaient les symptômes les plus rares. Sans intervention, les symptômes ont persisté pendant plus d'une semaine dans la moitié des cas. Dans les cas où l'on a repris le traitement à l'ISRS, les symptômes se sont résorbés dans les 72 heures. Dans certains cas, des symptômes de sevrage ont fait de nouveau leur apparition lorsqu'on a interrompu à nouveau le traitement au même ISRS. **Conclusions :** On a utilisé les constatations pour élaborer des critères de diagnostic du syndrome d'interruption du traitement à l'ISRS. Ces critères sont les suivants : au moins deux des symptômes suivants qui font leur apparition en moins d'un à sept jours suivant l'interruption du traitement ou la réduction de la posologie d'un ISRS après utilisation pendant au moins un mois, lorsque ces symptômes causent une incapacité ou une détresse significative sur le plan clinique et ne sont pas attribuables à un problème médical général ou à la réapparition d'un trouble mental : étourdissements, sensation légèreté, vertige ou sensation d'évanouissement; sensation ressemblant à celle d'un choc ou paresthésie; anxiété; diarrhée; fatigue; instabilité de la démarche; maux de tête; insomnie; irritabilité; nausées ou vomissements; tremblement et troubles de la vue.

Introduction

Many clinicians now consider selective serotonin reuptake inhibitors (SSRIs) the treatment of choice for patients with a number of psychiatric diagnoses, including mood, anxiety, eating, impulse-control and other disorders.[1] Therapeutic efficacy, simple dosing regimens, favourable side-effect profiles and relative safety in overdose have all contributed to their popularity.

When first introduced, SSRIs were not known to be associated with a discontinuation syndrome. However, with their widespread use, reports of symptoms appearing upon discontinuation or dosage reduction of these agents have emerged with increasing frequency. Recently, the concept of an SSRI discontinuation syndrome has received considerable support in the literature;[1–5] however, the specific criteria by which this phenomenon may be identified have not been established.

Our objective was to find all case reports of SSRI discontinuation symptoms and use them to provide a clinically useful description of SSRI discontinuation phenomena. In particular, we planned to use this information to develop diagnostic criteria for SSRI discontinuation syndrome.

Methods

We searched the MEDLINE and PSYCHLIT computerized databases (1986 to 1997) as well as references of relevant articles for all reports of discontinuation of fluoxetine, fluvoxamine, paroxetine or sertraline. We then reviewed the case reports identified, assessing demographic and treatment information, as well as information concerning the timing, duration, number, nature and frequency of discontinuation symptoms. If a single patient was reported to have experienced multiple episodes of SSRI discontinuation symptoms, we included only the initial episode. Symptoms that were present before and during SSRI treatment were not considered.

Results

Fifty-one cases were identified.[6–29] Two cases[20] were excluded from further review because, in this report of 4 patients experiencing symptoms after discontinuation of fluvoxamine, it was not clear in 2 instances which patients experienced which symptoms. Three cases[8,14] were excluded because other medication had been started or discontinued concurrently with SSRI taper or discontinuation. An open-label study,[30] a retrospective

chart review,[31] and a review of reports to the UK adverse drug reaction database[32] were also identified.

Case report data

In the 46 cases reviewed, 1 subject's sex was not identified; of the remaining 45 cases, 27 (60%) involved female subjects and 18 (40%) involved male subjects. Age was indicated for 39 of the 46 cases and ranged from 22 to 64 years.

All 46 cases reported the specific SSRI discontinued by the patient. Paroxetine was discontinued in 30 of the cases (65.2%),[7,9,11,12,14,15,17,22,23] sertraline in 8 (17%),[6,14,15,18,19,25] fluoxetine in 5 (11%)[8,10,13,26,27] and fluvoxamine in 3 (7%).[20,27]

The daily dosage of SSRI before taper or discontinuation was reported in 40 of the 46 cases and, in all cases, was within the range employed in clinical practice. The daily dosage of paroxetine (received by 28 patients) ranged from 10 to 60 mg, with 12 of the cases receiving 20 mg, and 6 of the cases receiving 60 mg. The reported daily dosage of sertraline ranged from 50 to 150 mg. The daily dosage of fluoxetine (2 cases) was 40 mg. The daily dosage fluvoxamine was 100 mg in one case and 300 mg in another case. The duration of treatment before discontinuation was reported in 38 of the 46 cases. All patients but 1 were treated for more than 1 month. The method of discontinuation was described in 44 of the 46 cases. In 23 of 44 cases (52%) the drug was tapered, whereas in the remaining 21 cases the discontinuation was abrupt.

Table 1: Symptoms occurring after discontinuing an SSRI (only those occurring in more than 5% of cases are included)

Symptoms	Number (and %) of reported cases with symptom $n = 46$	
Neurological		
Dizziness/light-headedness/vertigo	30	(65.2)
Gait instability	10	(21.7)
Shock-like sensations	6	(13.0)
Paresthesia	5	(10.9)
Visual disturbance	5	(10.9)
Loss of balance	4	(8.7)
Somatic		
Nausea/emesis	17	(37.0)
Fatique	12	(26.1)
Headache	11	(23.9)
Diarrhea	5	(10.9)
Myalgia	4	(8.7)
Chills	3	(6.5)
Mental		
Insomnia	8	(17.4)
Agitation	4	(8.7)
Impaired concentration	4	(8.7)
Vivid dreams or nightmares	4	(8.7)
Depersonalization/detachment/dissociation	3	(6.5)
Irritability	3	(6.5)
Suicidal thoughts or behaviour	3	(6.5)

Timing of symptom onset was reported in 42 of the 46 cases. In 10 of 42 cases (23.8%), onset of symptoms began during taper. In the remaining 32 cases (76.2%), symptoms began after SSRI discontinuation. In the cases in which symptoms began after the SSRI was stopped, most patients (81.3%) experienced symptom onset within 1 to 3 days; 93.8% had symptom onset within 1 week; and all had symptoms develop within 2 weeks.

Fifty-three different symptoms were reported in the 46 case reports. The number of symptoms per case ranged from 1 to 12, with a mode of 1 to 2 symptoms. Another lesser peak appeared at 5 symptoms per case. Nineteen symptoms were reported in more than 5% of the cases (Table 1). Dizziness (and its variants, such as light-headedness, feeling faint or vertigo) was the most common single symptom. Other symptoms frequently reported included nausea or emesis, fatigue, headache, gait instability and insomnia. Notable for their unusual quality were sensory symptoms such as shock-like sensations, paresthesia and a variety of visual disturbances. Neurologic symptoms were most frequently reported.

Forty-five cases included information concerning symptom resolution. In 26 of 45 cases (57.9%) symptoms resolved spontaneously, whereas in 17 of 45 cases (37.8%) resolution followed an increased dosage or reintroduction of the SSRI. In 11 of 26 cases (47.6%), symptoms resolved in less than 1 week. In the rest of the cases, symptoms were of longer duration (up to 13 weeks in 1 case of sertraline discontinuation). In the cases in which the SSRI was restarted or the dosage increased, symptoms resolved completely within 24 hours in 8 of 12 cases (66.7%), and within 72 hours in all 12 cases. In 15 of the 46 reported cases, information was supplied concerning subsequent discontinuation of the same SSRI. In 11 of the 15 cases (73.3%), patients experienced recurrence of withdrawal symptoms that were remarkably similar with each episode.

Review of other studies

Price et al[32] studied 430 reports in the UK adverse drug reaction database for withdrawal reactions following discontinuation of fluoxetine, fluvoxamine, paroxetine or sertraline. They found that the reporting rate with paroxetine was 10 times higher than with sertraline and

fluvoxamine, and 100 times higher than with fluoxetine. The final dose of paroxetine was 20 mg in 73% of reported cases. Table 2 summarizes the 906 symptoms reported. General symptoms (the most common being dizziness) was the most frequent category, with neuropsychiatric/psychological (the most common being anxiety) the next most frequent. Sensory symptoms (the most common being paresthesia), motor effects (the most common being tremor) and gastrointestinal symptoms (the most common being nausea), also accounted for 10% or more of the total symptoms reported. The median period between stopping treatment with paroxetine and the onset of symptoms was 2.1 days. The duration of symptoms in patients not reported to have been treated was 1 to 52 days (mean 10 days, standard deviation 10 days).

Black et al[30] systematically evaluated symptoms in 14 subjects abruptly withdrawn from fluvoxamine treatment. New symptoms developed in 12 subjects (86%). Symptoms peaked on Day 5 post-discontinuation, when dizziness/uncoordination, headaches, nausea or irritability were reported in more than 25% of subjects.

Coupland et al[31] studied discontinuation symptoms in a retrospective chart review of 171 patients who discontinued an SSRI while under supervision. At least 1 new symptom developed in 21 patients, who were therefore considered to be cases. The incidence of SSRI discontinuation symptoms was highest in subjects receiving paroxetine (20%) and fluvoxamine (14%). The onset of symptoms occurred 2 to 3 days (no later than 5 days) after the last dose of medication, and on occasion it occurred during taper. All cases reported either dizziness, paresthesia, or, in 1 case, nightmares, as the most prominent symptom.

Table 2: Symptoms following discontinuation of an SSRI reported to the UK adverse drug reaction database*

System category	Number (and %) of reported cases
General†	298 (32.9)
Neuropsychiatric, psychological‡	216 (23.8)
Sensory changes§	134 (14.8)
Gastrointestinal¶	106 (11.7)
Motor effects**	102 (11.3)
Other††	50 (5.5)

*Recalculated from Price et al[32]
†Including dizziness, light-headedness, sweating, headache, insomnia; most common being dizziness
‡Including paresthesia, numbness and visual disturbance; most common being paresthesia
§Including imbalance and tremor; most common being tremor
¶Including anxiety, agitation, hallucinations, confusion and mood changes; most common being anxiety
**Mainly nausea
††Most common being palpitations

Discussion

SSRI discontinuation syndrome may be relatively common. Coupland et al[31] reported at least 1 new symptom in 20% of patients who had discontinued paroxetine and in 14% of patients who had discontinued fluvoxamine. Black et al[30] reported new symptoms in 86% of 14 subjects who had abruptly discontinued fluvoxamine.

SSRI discontinuation symptoms occur in a variety of clinical circumstances. In the cases reviewed, symptoms were reported in patients of both sexes and of different ages. Indications for initial SSRI treatment ranged from the common (mood and anxiety disorders) to the uncommon (such as stuttering[9]). The syndrome developed after SSRI discontinuation at doses that ranged from low to high within the range employed in clinical practice.

There were case reports of symptoms following the discontinuation of all 4 SSRIs, but symptoms were most often reported with paroxetine discontinuation. Coupland et al[31] and Price et al[32] also found paroxetine to be implicated with a high frequency. The simplest explanation may be that this reflects more frequent prescribing of paroxetine, but other hypotheses have been put forward.[5] One explanation is pharmacokinetic — paroxetine has a short half-life and no active metabolites. Another explanation is pharmacodynamic — paroxetine has an affinity for cholinergic receptors similar to the tricyclic antidepressants (TCAs), raising the possibility of cholinergic rebound on discontinuation. Symptoms of cholinergic rebound include malaise, nausea or emesis, diarrhea, diaphoresis, restlessness and insomnia.[33–35] However, cholinergic rebound does not account for the full spectrum of symptoms that commonly follow paroxetine discontinuation, in particular, neurologic symptoms such as dizziness, paresthesia, shock-like sensations and gait instability.

Citalopram, the SSRI that most recently became available in Canada, was not included in our review. However, Lundbeck's Canadian monograph for this drug does describe discontinuation symptoms, which occurred when citalopram was abruptly stopped after 8 weeks of treatment.[36]

How does one diagnose SSRI discontinuation syndrome? The patient has usually been receiving the drug for 1 month or more, and symptoms usually develop

within 3 days of SSRI discontinuation or dose reduction. To assist with the diagnosis of this syndrome, we have summarized the information obtained from case reports in the form of proposed diagnostic criteria (Table 3).

Symptoms listed in the B criteria were reported with a frequency of at least 10% in the cases we reviewed. Three other symptoms (anxiety, irritability and tremor) were added to reflect the findings of the other studies reviewed.[30–32]

The D criteria in Table 3 encourage the physician to consider a differential diagnosis whenever new symptoms emerge in the context of an SSRI being discontinued. In general, symptoms of recurrence of the original psychiatric illness are more likely to emerge weeks rather than days after the discontinuation of an SSRI.[37] Physicians' awareness of some of the more unusual symptoms of this syndrome, such as dizziness and shock-like sensations, should prevent the unnecessary medical investigations described in some cases.[1,8,24,25,29]

Our review suggests that SSRI discontinuation syndrome may occur even if the SSRI dose is tapered. In approximately half of the cases reported, an attempt had been made to taper the SSRI, although details concerning the duration and rapidity of taper were not consistently provided. At this point, it seems unclear whether tapering an SSRI routinely will prevent discontinuation symptoms.

Table 3: Proposed diagnostic criteria for SSRI discontinuation syndrome

Criterion	Description
A	Discontinuation of or reduction in dose of an SSRI after a period of use of at least 1 month
B	Two (or more) of the following, developing within 1 to 7 days of criterion A: Dizziness, light-headedness, vertigo or feeling faint Shock-like sensations or paresthesia Anxiety Diarrhea Fatigue Gait instability Headache Insomnia Irritability Nausea and/or emesis Tremor Visual disturbances
C	The symptoms in Criterion B cause clinically significant distress or impairment in social, occupational or important areas of functioning
D	The symptoms are not due to a general medical condition and are not better accounted for by recurrence of symptoms of the mental disorder for which the SSRI was originally prescribed, or by concurrent discontinuation (or reduction in use) of another psychoactive substance

Once discontinuation symptoms occur, there are essentially 2 treatment approaches, both of which have limitations. One approach is to restart the drug, since symptoms resolve rapidly following reinstitution of an SSRI. The problem with this is that there may be clinical indications to discontinue the SSRI. Also, the syndrome tends to recur when the same SSRI is later discontinued. Almost 75% of patients in reported cases of restarting the drug experienced recurrence of the syndrome when attempts were made to discontinue the same SSRI on another occasion. The alternative approach is to allow the syndrome to run its course. Although about half of patients should experience resolution of symptoms within a week, a significant number may experience symptoms for several weeks. Under these circumstances, patients should be educated as to the nature of the symptoms and reassured that they will resolve.

The major limitation of this review is that, in constructing our diagnostic criteria, we have relied heavily on information derived from published case reports, which are of variable quality and based on open and unsystematic observations. The number of reported cases is relatively few, and a number of biases may have influenced which cases and which symptoms have been reported. We tried to address these problems by also reviewing the findings of studies that have employed other methodologies to investigate the phenomenon. Particular attention was paid to the analysis by Price et al,[32] because of their large database of 430 spontaneous adverse drug reaction reports, and to the study by Black et al,[30] because of the prospective and systematic way in which symptoms were measured. The findings of these studies were compatible with ours, in that dizziness was the commonest symptom in all, while gait imbalance, headache, insomnia, nausea and paresthesia were also commonly reported across the studies. However, there was some discrepancy, in that these studies also reported a high frequency of anxiety, irritability and tremor, a finding not reflected in our case report review. This is likely because mild or nonspecific symptoms such as these may not have warranted a case report. The discrepancy was addressed by inclusion of these symptoms in our B criteria.

Finally, one needs to address the question of whether the SSRI discontinuation syndrome is distinct from other antidepressant discontinuation syndromes, since new symptoms following the discontinuation of tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) are well described.[38–41]

Syndromes induced by discontinuation of TCAs include (1) generalized somatic and psychological distress, (2) sleep disturbance, (3) movement disorders, and (4) affective disorders.[38] Category (1) and (2) symptoms that overlap with our B criteria symptoms include anxiety, diarrhea, fatigue, headache, insomnia and nausea. Movement disorders associated with discontinuation of TCAs are rare, but are usually parkinsonism or akathisia. Dizziness (and variants), paresthesia, shock-like sensations, gait instability and visual disturbances do not appear to be common in TCA withdrawal. There is a report of "possible paresthesia," dizziness and "disorientation in space" following discontinuation of clomipramine, but clomipramine is a potent SRI.

Symptoms associated with the discontinuation of MAOIs characteristically involve cognitive impairment, which is not frequently described following SSRI withdrawal.[38] Psychosis and severe depressed mood have also been described. The symptoms associated with MAOI discontinuation that do overlap with our B criteria symptoms include anxiety, ataxia, fatigue, insomnia, irritability and visual disturbances. Again, dizziness, paresthesia and shock-like sensations are not commonly described following MAOI discontinuation.

Thus, although some of the symptoms that accompany the discontinuation of SSRIs overlap with those following TCA or MAOI discontinuation, the neurologic symptoms of dizziness, paresthesia and shock-like sensations appear to be particularly characteristic of SSRI discontinuation syndrome. Dizziness, being both common and distinctive, is a particularly prominent feature of the syndrome.

Conclusions and recommendations for future research

Using case report data, and after review of other studies of the phenomenon, we are proposing diagnostic criteria for the SSRI discontinuation syndrome. The validity of these criteria, particularly the B criteria, need to be tested. The clinical value of diagnostic criteria is that they may facilitate recognition of SSRI discontinuation symptoms. From the perspective of clinical practice, it is also important to determine whether tapering SSRIs reduces the incidence of discontinuation symptoms and can prevent a syndrome that is distressing and somewhat problematic to treat.

These questions could be addressed in a study that prospectively identifies symptoms in a patient group in which an SSRI is discontinued either abruptly or in a tapered fashion over several weeks. This would permit determination of the incidence of discontinuation symptoms with and without tapering and also the systematic evaluation of all symptoms present.

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