

Selective Serotonin Reuptake Inhibitor Discontinuation Symptoms

R Mahendran,**FAMS, M Med (Psych), DPM*, A Chan,***FAMS, MBBS, M Med (Psych)*

Abstract

This paper reviews the literature on selective serotonin reuptake inhibitor discontinuation symptoms. These symptoms have been well described in numerous anecdotal case reports and reports of small series of cases in the Caucasian population. There are no reports in the literature of it occurring in Asian patients. A study involving 65 patients on this type of antidepressant revealed that Asian patients do experience these withdrawal symptoms as well. Seven patients (3 on fluoxetine, 4 on fluvoxamine) reported symptoms similar to those reported by Caucasian patients in the literature. Three of the cases are reported in detail to highlight the clinical presentation in such cases.

Ann Acad Med Singapore 1999; 28:596-9

Key words: Discontinuation symptoms, Physical symptoms, Psychological symptoms, Selective serotonin reuptake inhibitors (SSRI)

Introduction

Selective serotonin reuptake inhibitors (SSRIs) are a new class of antidepressants which are effective, better tolerated with less side effects and more specific in receptor activity than the older tricyclic antidepressants. However, like tricyclic antidepressants and other groups of antidepressants such as the monoamine oxidase inhibitors (MAOIs) and the newer norepinephrine-serotonin-dopamine agents like venlafaxine, SSRIs are associated with discontinuation symptoms.¹⁻³ Studies on medication compliance indicate that many patients do not comply fully with their medication regimes.⁴ This increases their risk for experiencing discontinuation symptoms.

Discontinuation symptoms with SSRIs can occur in various ways:

1. after routine discontinuation of treatment during dose reduction;
2. on abrupt discontinuation;
3. after switching antidepressant treatments; or
4. in the patient who misses antidepressant doses.*

Antidepressant discontinuation symptoms include somatic, gastrointestinal and psychological abnormalities.⁵ Those associated with SSRI discontinuation, however, tend to be physical rather than psychological.⁶ Five clusters of somatic symptoms have been reported (Table I). In addition to novel symptom clusters like problems with balance and sensory abnormalities, SSRI discontinuation could also be associated with aggressive and impulsive behaviour.⁷ Gillespie et al, in a presentation at

the 1996 World Congress of Psychiatry (unpublished data), reviewed all publications of SSRIs discontinuation in the literature up to July 1996 and found the frequency of symptoms to be as high as 45% for neurological symptoms. Gastro-intestinal and symptoms of somatic distress occurred in 27% of cases, neuropsychiatric or behavioural symptoms in 23% of cases and symptoms of sleep disturbance in 5%.

The discontinuation symptoms are generally mild and transient for the SSRIs and the tricyclic antidepressants but may be serious for the MAOIs.⁶ The different pharmacokinetic and pharmacodynamic profiles of SSRIs determine variation in incidence of discontinuation symptoms (Table II).⁸ They are much more common with a shorter acting SSRI, for example paroxetine, than with a longer acting SSRI like fluoxetine.⁹ However discontinuation symptoms can be severe and chronic and may have a major impact on the patient.

Importantly SSRI discontinuation symptoms include symptoms that mimic the very disorders for which the SSRI was first prescribed. The difficulty is in recognising

TABLE I: CLUSTERS OF SOMATIC SYMPTOMS⁶

Cluster	Examples
Disequilibrium	Dizziness, vertigo, ataxia
Gastrointestinal symptoms	Nausea, vomiting
Flu-like symptoms	Fatigue, lethargy, myalgia, chills
Sensory disturbances	Paresthesia, sensations of electric shock
Sleep disturbances	Insomnia, vivid dreams

* Consultant Psychiatrist

** Senior Registrar

Woodbridge Hospital & Institute of Mental Health

Address for Reprints: Dr R Mahendran, Woodbridge Hospital & Institute of Mental Health, 10 Buangkok View, Singapore 539747.

TABLE II: PHARMACOKINETICS OF SSRIs⁸

SSRI	Autoinhibitor of metabolism	Half-life (single dose)	Half-life (multiple dose)	Linearity of P'Kinetics
Paroxetine	Yes	10H	21H	Non-linear
Fluvoxamine	Yes	11H	14H	Non-linear
Sertraline	No	26H	26H	Linear
Citalopram	No	33H	33H	Linear
Fluoxetine	Yes	1.9D	5.7D	Non-Linear

the phenomena and not mistakenly concluding that the patient has had a relapse, exacerbation of symptoms or poor response to treatment.⁵

Studies have shown variable time courses for SSRI discontinuation symptoms. Price et al¹⁰ examined the UK database of adverse drug reactions associated with fluoxetine, fluvoxamine, paroxetine and sertraline. Withdrawal symptoms usually occurred after 2 days and lasted for an average of 10 days. However Coupland's retrospective chart review of 352 patients revealed that symptoms could persist for up to 21 days (mean 11.8 days) after onset.⁹

There are few large studies of SSRI withdrawal in the literature. Blomgren et al (unpublished data) designed a study akin to episodes during which patients forget to take their medication. In this study, two hundred and twenty patients received placebo drugs double blind over 5 to 8 days. This study found that patients treated with fluoxetine spontaneously reported fewer discontinuation symptoms than patients treated with either sertraline or paroxetine.

Most of the literature on SSRI discontinuation symptoms is in anecdotal case reports. The most number of reports have occurred with paroxetine^{11,12} and sertraline.^{13,14} There are fewer reports with fluvoxamine¹⁵ and fluoxetine^{16,17} and recently with venlafaxine as well. Earlier reviews found that the number of cases of withdrawal symptoms identified from the literature up to July 1996 was 129 for paroxetine, 15 for sertraline and 8 for fluoxetine.

Our review of the literature on SSRI discontinuation symptoms revealed that all the reports to date involved Caucasian patients. In a study undertaken at a psychiatric hospital in Singapore, consecutive patients on SSRIs attending a clinic for anxiety and mood disorders and other psychiatric clinics during a month long period, under the care of the investigators, were studied for SSRI discontinuation symptoms. Approval was sought from the hospital's Ethics Committee and patients' participation was voluntary. A total of 65 patients agreed to be interviewed. Spontaneous reports of SSRI discontinuation symptoms were noted and a checklist of commonly reported discontinuation symptoms was also used.

Results

The cohort consisted of 28 male and 37 female patients of whom 41 had a diagnosis of depression and 16 a diagnosis of a neurotic disorder. The majority were Chinese (52 patients) and 42 patients were married. Their ages ranged from 20 to 67 years with two-thirds of them in the 31 to 50 years age range. Of the 65 patients, 32 were on fluoxetine in the 10 to 40 mg dose range, 25 were on fluvoxamine in the 50 to 200 mg dose range, 7 were on citalopram, receiving 10 to 30 mg and 1 patient was on sertraline, receiving 50 mg per day. None was on paroxetine.

Of the 65 patients, 9 had discontinued their SSRIs at one time or another and of these, only in 1 case was it the doctor's decision to stop the medication. Of the 9 patients, 4 were on fluoxetine, 4 on fluvoxamine and 1 patient on citalopram. The patient on citalopram stopped taking her SSRI abruptly but she was also on diazepam and lorazepam at that time which she continued taking and did not experience withdrawal symptoms. One of the patients on fluoxetine also did not experience any withdrawal symptoms. In this patient, the fluoxetine was gradually tapered by her psychiatrist. The remaining 7 patients experienced withdrawal symptoms. These are listed in Table III.

TABLE III: SSRI DISCONTINUATION SYMPTOMS IN THE PATIENTS STUDIED

Patient	Medication	Dose	Symptoms
1	Fluvoxamine	100 mg	Giddiness, numbness, episodes of nervousness
2	Fluvoxamine	200 mg	Vertigo, lightheadedness, weakness, unsteady gait, numbness, paresthesia in the legs, hyperacusis
3	Fluvoxamine	200 mg	Flu-like symptoms, cold sensation, agitation
4	Fluvoxamine	100 mg	Insomnia, agitation
5	Fluoxetine	20 mg	Fatigue, irritability, vivid dreams
6	Fluoxetine	20 mg	Forgetfulness
7	Fluoxetine	20 mg	Fatigue, irritability, vivid dreams, muscle aches and pains, agitation, confusion, forgetfulness

Case Reports

The first 3 cases in Table III are reported in detail to reflect their clinical presentations.

Case 1

Patient A, a 36-year-old Indian man had anxiety symptoms for about 10 months with depressed mood and suicidal thoughts for 3 of these months. He had a previous episode of "nervousness" about 10 years ago which

lasted about 6 months and during which he was treated by his private practitioner.

A was diagnosed as suffering from an anxiety disorder (not otherwise specified) (DSM IV); clinically he had significant symptoms of both anxiety and depression. He was prescribed tab fluvoxamine 100 mg at night and diazepam 2 mg in the morning and afternoon and 10 mg for the night. Two weeks later, the diazepam was reduced to 1 mg in the morning and 5 mg at night. He was also referred for anxiety management training. Two months after his first visit, he was no longer depressed or suicidal but began to report new symptoms of giddiness and numbness and episodes of nervousness. He also complained of feeling tired and blur. He claimed he was taking the medication and blamed the medication for worsening his nervousness.

At the start of the treatment, the patient had a great deal of anxiety about taking medication and had needed a lot of explanation and persuasion as to how the medication would relieve his symptoms and also his fears about becoming an "addict" had to be allayed. On close questioning about compliance with medication, the patient finally admitted he had reduced his dose as he felt better to just three or two times a week. About 2 days after the last dose he would experience symptoms of giddiness, numbness and nervousness. These would resolve after about 2 days if he did not take his medication.

Case 2

Patient B, a 41-year-old Eurasian man with an obsessive compulsive disorder diagnosed 5 years previously, characterised by obsessive rumination and doubts and underlying obsessional personality traits. He was on fluvoxamine 200 mg per day for about a year when he abruptly discontinued medication and after 6 days he experienced nausea, giddiness and headaches and his legs felt "wobbly" "as if legs were going to fall off" and he experienced hyperacusis. He was seen 4 days after the onset of symptoms at which stage he was very anxious and frightened by the symptoms he was experiencing. He was restarted on medication with relief of symptoms after about 3 days.

Case 3

Patient C, a 36-year-old Malay lady with history of migraine since her teens, became depressed in July 1997 and complained of poor memory and feeling frightened. This was precipitated by news of her former boyfriend's death. She exhibited childish regressive behaviour and claimed she could not remember her husband, children or any other family members. She was diagnosed as suffering from depressive illness with dissociative disorder. She was prescribed tab fluvoxamine which was gradually increased to 200 mg. About 5 months after

starting treatment, she began to omit doses as she felt "fine". On one occasion after 5 days without fluvoxamine, she suddenly felt agitated in the office and felt cold and started to shiver. She became so distressed that she began to cry and had to return home as she was unable to work. She took her medication and slept. She awoke the next day with none of the symptoms.

Discussion

Although this study is a small review of 65 patients on SSRIs, it shows that discontinuation symptoms do occur even in our local patients on SSRI. They are a real problem and play an important role in patient management. The first case highlights one of the first problems that of the difficulty in recognising the phenomena and distinguishing it from the underlying illness in a patient who occasionally misses out a few doses of medication. The second case highlights the occurrence of novel discontinuation symptoms with fluvoxamine when the patient abruptly discontinued treatment. The third case reflects the need to educate patients about discontinuation symptoms and to warn against abruptly discontinuing medication.

It is not possible to draw any conclusions about the SSRIs themselves and the incidence. This is because SSRI use was determined by the restricted formulary practice. There were no patients on paroxetine in our cohort and this was the most commonly reported SSRI with discontinuation symptoms in the literature. Most of our patients were on fluoxetine and fluvoxamine. The findings serve as a reminder of the existence of discontinuation symptoms and the need for vigilance on the part of the psychiatrist.

The mechanism of action for these discontinuation symptoms is not clearly understood. It is known that long-term treatment with SSRI is associated with down-regulation of 5HT₂ receptors and desensitisation of both the 5HT₂ receptor transmembrane signalling system and 5HT auto receptors. Researchers have suggested that these features associated with the sudden decrease of serotonin levels could cause the symptoms. There is also the hypothesis that some symptoms associated with paroxetine discontinuation (which are similar to tricyclic antidepressant discontinuation) may be caused by cholinergic rebound.*

SSRIs with a short half-life may be an important risk factor for SSRI discontinuation symptoms. In addition, those patients on high doses, as well as on treatment for a long period, may be at increased risk.

The clinician needs to be alert to possible occurrence of discontinuation symptoms and patients should be educated especially those at risk of not complying with regular treatment. These patients need to be reassured that the symptoms are short-lived. For the clinician, gradual and close monitoring of SSRI taper is important.

Mild symptoms can often be treated by simple reassurance that they are transient but for more severe symptoms, it may be necessary to reinstitute the dosage of the original antidepressant and slow the rate of taper.¹⁸

REFERENCES

1. Lejoyeux M, Adès J. Antidepressant discontinuation: a review of the literature. *J Clin Psychiatry* 1997; 58:11-6.
2. Zajecka J, Tracy K A, Mitchell S. Discontinuation symptoms after treatment with serotonin reuptake inhibitors: A literature review. *J Clin Psychiatry* 1997; 58:291-7.
3. Rauch S L, O' Sullivan R L, Jenike M A. Open treatment of obsessive compulsive disorder with venlafaxine: a series of ten cases [letter]. *J Clin Psychopharmacol* 1996; 16:81-4.
4. Keck P E Jr, McElroy S L, Strakowski S M. Factors associated with pharmacologic noncompliance in patients with mania. *J Clin Psychiatry* 1996; 57:292-7.
5. Discontinuation of antidepressant therapy: Emerging complications and their relevance. *Neuroscience Reporter* 1997 Apr 25.
6. Schatzberg A F, Haddad I', Kaplan E M, Lejoyeux M, Rosenbaum J F, Young A H, et al. Serotonin reuptake inhibitor discontinuation syndrome: A hypothetical definition. *J Clin Psychiatry* 1997; 58:5-10.
7. Haddad P. Newer antidepressants and the discontinuation syndrome. *J Clin Psychiatry* 1997; 58:17-21.
8. Lane R M. Withdrawal symptoms after discontinuation of selective serotonin reuptake inhibitors (SSRIs). *J Serotonin Res* 1996; 3:75-83.
9. Coupland N J, Bell C J, Potokar J P. Serotonin reuptake inhibitor withdrawal. *J Clin Psychopharmacol* 1996; 16:356-62.
10. Price J S, Waller P C, Wood S M, Mackay A V. A comparison of the postmarketing safety of 4 SSRIs including the investigation of symptoms occurring on withdrawal. *Br J Clin Pharmacol* 1996; 42:757-63.
11. De Battista C, Schatzberg A F. Physical symptoms associated with paroxetine withdrawal [letter]. *Am J Psychiatry* 1995; 152:1235-6.
12. Barr L C, Goodman W K, Price L H. Physical symptoms associated with paroxetine discontinuation. *Am J Psychiatry* 1994; 151:289.
13. Dominguez R A, Goodneck P J. Adverse events after sertraline discontinuation of paroxetine. *Pharmacotherapy* 1995; 15:778-80.
14. Leiter F L, Nirenberg A A, Sanders K M. Discontinuation reactions following sertraline. *Biol Psychiatry* 1995; 38:694-5.
15. Benazzi F. SSRI discontinuation syndrome related to fluvoxamine [letter]. *J Psychiatry Neurosci* 1998; 23:94.
16. Berlin C S. Fluoxetine withdrawal symptoms [letter]. *J Clin Psychiatry* 1996; 160:283-4.
17. Stoukides J A, Stoukides C A. Extrapyramidal symptoms upon discontinuation of fluoxetine [letter]. *Am J Psychiatry* 1991; 148:1263.
18. Rosenbaum J F, Zajecka J. Clinical management of antidepressant discontinuation. *J Clin Psychiatry* 1997; 58:37-40.