SELECTIVE SEROTONIN REUPTAKE INHIBITOR DISCONTINUATION SYNDROME: TWO CASE REPORTS

Lut Tamam, M.D*, Nurgül Özpoyraz, M.D*

SELEKTİF SEROTONİN GERİ-ALIM İNHİBİTÖRLERİ KESİLME SENDROMU: İKİ OLGU SUNUMU

ÖZET

Bu yazıda, selektif serotonin geri-alım inhibitörleri (SSRI) ile tedavi edilirken tedavilerini âniden sonlandıran ve sonrasında SSRI kesilme sendromu geliştiren iki olgu sunulmuştur. Her iki hastada SSRI kesilmesine bağlı olarak çeşitli somatik ve psikiyatrik belirtiler ortaya çıkmıştır. Bulantı, kusma, baş ağrısı, uyku bozuklukları ve baş dönmesi her iki hastada saptanan bulgulardı. Kesilme belirtileri ilâç kesildikten sonraki üç günde ortaya çıkmış, aynı SSRI'ın hemen tekrar başlanması ile sona ermiştir. Olgularda saptanan bu tablolar, SSRI tedavisi sırasındaki uyumun önemini bir kez daha vurgulamaktadır. Bâzen tek bir SSRI dozunu dahi atlamak, hastalarda kesilme belirtilerine neden olabilir, bu durumda daha önce sonlandırılmış bir tedavinin yeniden başlamasına, dozajda artışa, gereksiz yeni ilâç eklenmesine veya fiziksel incelemelere yol açabilir. SSRI ile tedavi sürecinde ortaya çıkan yeni belirtilerin nedeninin SSRI kesilme sendromu olabileceği her zaman akılda bulundurulmalıdır.

Anahtar Kelimeler: SSRI, depresyon, paroksetin, fluvoksamin, geri çekilme sendromu

ABSTRACT

Two cases that developed selective serotonin reuptake inhibitor (SSRI) discontinuation syndrome after abrupt cessation of therapy are presented in this article. The patients who have been receiving two different SSRIs (paroxetine and fluvoxamine) for their psychiatric disorders stopped their treatment abruptly without noticing their physicians, which leaded to the onset of a cluster of somatic and psychological symptoms within three days after discontinuation. Nausea, vomiting, headache, sleep disturbances and dizziness were symptoms encountered in both cases. The patients experienced SSRI discontinuation symptoms up to 3 days after the onset of syndrome. Symptoms resolved upon reinitiating of the same SSRI. These cases emphasize the importance of compliance of the patients with SSRI treatment. Missing even a dose of an SSRI might lead to discontinuation syndrome which might in turn lead to recommencement of a discontinued treatment, an increase in dosage, a change in the drug, addition of a new drug and unnecessary physical assessments. SSRI discontinuation syndrome should be borne in mind in assessment of newly emerging symptoms during SSRI treatment.

Keywords: selective serotonin reuptake inhibitors, depression, paroxetine, fluvoxamine, discontinuation syndrome

INTRODUCTION

Selective serotonin reuptake inhibitors (SSRIs) [fluoxetine, fluvoxamine, paroxetine, sertraline and citalopram] have been effectively used in the long-term treatment of several different mental disorders including depression and Obsessive Compulsive Disorder in recent years (Haddad 1998, Tamam and Ozpoyraz 2002). Parallel to the widespread extended use of SSRIs, there were reports of several side effects that were not determined or observed during short-term drug-efficacy trials. One such entity is the "SSRI discontinuation syndrome", which has drawn significant research interest in recent years (Price et al. 1996, Lejoyeux and Ades 1997, Stahl et al. 1997, Zajecka et al. 1997, Black et al.2000). Appearing at first in case reports (Coupland et al. 1996, Haddad 1998, Diler et al. 2000), SSRI discontinuation syndrome has now been noted in several different controlled studies (Rosenbaum et al. 1998, Olver et al. 1999, Michelson et al. 2000, Bogetto et al. 2002).

SSRI discontinuation syndrome consists of several characteristics signs and symptoms that follow the cessation or dose reduction of the related drugs (Olver et al. 1999, Schatzberg et al. 1997a). These symptoms are generally self-limiting, resolve rapidly after recommencement of SSRIs and cannot be explained by a recurrence of the disorder being treated (Haddad 1998). Depending on the clinical relevance and frequency of reported discontinuation symptoms, several authors (Haddad 1998, Black et al. 2000) have proposed diagnostic criteria for SSRI discontinuation syndrome. In a recent study Black and his friends (2000), defined the diagnostic criteria for this syndrome as follows: Appearance of two or more of the following symptoms (i.e. dizziness, lightheadedness, vertigo, or feelings of fainting; nausea and/or emesis; headache; visual disturbances; anxiety; shock like sensations or paraesthesia; tremor; fatigue; insomnia; irritability; gait instability; and diarrhea) within 1 to 7 days of discontinuation or reduc-

*Assistant Professor of Psychiatry, Çukurova University, Faculty of Medicine, Department of Psychiatry, Adana, Turkey / Çukurova Universitesi Tıp Fakültesi, Psikiyatri Anabilim Dalı, 01330, Balcalı, Adana, Turkey / Phone: 90-533-6306006 / Fax: 90-322-3386505 / E-mail: Ltamam@mail.cu.edu.tr , Ltamam@yahoo.com
**Professor of Psychiatry, Çukurova University, Faculty of Medicine, Department of Psychiatry, Adana, Turkey

tion in dose of an SSRI after at least one month's use. These symptoms should cause clinically significant distress in major areas of functioning and should not be due to a general medical condition or not better accounted for by recurrence of the mental disorder or by concurrent discontinuation of another psychoactive substance.

Though an effect of SSRI class (Tamam and Ozpoyraz 2002), a "SSRI discontinuation syndrome-like syndrome" could also emerge after discontinuation of several other antidepressants affecting the serotonergic system such as venlafaxine (Boyd 1998), nefazodone (Rajagopalan and Little 1999) and mirtazapine (Benazzi 1998). The incidence of SSRI discontinuation syndrome are reported to range between 35% and 86% in controlled studies while these figures are much lower in databases based on spontaneously reported adverse drug events (Stahl et al. 1997, Michelson et al. 2000). This discrepancy most probably suggests either lack of recognition of this phenomenon by treating physicians, underreporting of discontinuation symptoms or both (Young and Currie 1997). A recent survey (Young and Currie 1997) conducted among psychiatrists and general practitioners (GPs) revealed that 72% of the psychiatrists and 30% of GPs were aware that patients might experience antidepressant discontinuation symptoms. One other prominent contributing factor in occurrence of the discontinuation syndrome is noncompliance of the patients with the antidepressants prescribed (Kaplan 1997). This factor combined with lack of recognition of this phenomenon by the involved physicians increase and prolongs unwanted effects of discontinuation syndrome.

In this article we presented two cases that developed SSRI discontinuation syndrome as a result of non-compliance to treatment due to several reasons.

CASE REPORTS

Case I

Mr. A, 54-year old man with a DSM-IV diagnosis of Major Depressive Disorder was given treated with fluvoxamine 100 mg/day. The treatment continued for 3 months in outpatient clinic with a fluvoxamine dose of 200 mg/day. He did not receive any concomitant drug during this therapy except for two weeks of hydroxyzine 25 mg/day to treat his insomnia initially. At the control visit in the third month, he reported to feel much better than he used to at his first referral. He showed prominent improvement in interpersonal relations, sleep and appetite. It was noted that his depressive state was very much improved when compared with the first examination in the patient's file. He did not come to his scheduled appointment one month later (i.e. 4th month). Five days after his appointment, he presented to outpatient clinic agitated, reporting that he felt nervous and anxious for the last couple of days with sudden outbursts of anger towards his wife and children. He had trouble in sleeping with occasional nightmares further disturbing the sleep. He also developed headache, dizziness, nausea and vomiting with stomach cramps and several occasions of shortness of breath. According to the patient, these symptoms had developed 72 hours after his final dose intake. The patient confirmed after a detailed inquiry for compliance that he stopped the treatment, as he believed to be cured finally. The patient and his relatives deny use of alcohol or any illicit drug during this period. Fluvoxamine, 100 mg/day was reinstated immediately which resulted in resolution of discontinuation syndromes within 2 days with partial improvement in the first 12 hours. Mr. A has been followed up for six more months with a fluvoxamine dose of 200 mg/day resulting in total resolution of depressive symptoms. He did not experience or report such symptoms during the rest of the treatment. The therapy was discontinued gradually in 3 months at the end of the study with a final dose of 25 mg for the last 15 days. He did not experience any discontinuation syndrome during and three months after the cessation period.

Case II

Mrs. B, a 25-years old woman with a diagnosis of Major Depressive Disorder and Generalized Anxiety Disorder was switched to paroxetine by her psychiatrist after an initial treatment of clomipramine (150 mg/day) for the last three months. Because of side effects such as sedation and severe constipation, she requested a change that was endorsed by her psychiatrist. After two months of paroxetine treatment with a daily dose of 20 mg, marked improvement in clinical depressive symptoms especially in her appetite, anxiety and sleep quality had been observed. No side effects related with paroxetine were reported during this period. She was also administered 1 mg per day of alprazolam in an as required basis during the first month of treatment. No other drug was prescribed or used by patient after the first month. At fourth month of treatment, as she forgot to bring her medication with herself to a four-days holiday away from home, she did not receive her scheduled drugs. Thirty hours after missing her last daily dose, she experienced dizziness, tiredness, poor concentration, nausea, severe headache, insomnia, paraesthesias, flu-like symptoms and gait disturbances. Three days later she applied to our outpatient clinics noting that her symptoms all recurred and were intensified. Detailed assessment revealed her temporary non-compliance with paroxetine. Paroxetine 20 mg was administered immediately and a daily dose of paroxetine 20 mg was re-introduced. Her discontinuation syndrome subsided in 24 hours and completely disappeared within 48 hours of recommencing SSRI treatment. She compliantly continued her

treatment thereafter. Six months later paroxetine dose was decreased gradually (5 mg per week) and stopped suitably. Her four months follow up after cessation of therapy did not display any discontinuation symptoms ever since.

DISCUSSION

Since the introduction of antidepressants into the market over the past four decades, discontinuation syndromes have been frequently reported with these drugs especially for tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOI), SSRIs and lately serotonin noradrenergic reuptake inhibitors (SNRIs) and other serotonergic drugs (mirtazapine and nefazodone) (Coupland et al. 1996). Various studies have described SSRI discontinuation syndromes consisting of 10 to 53 different somatic or psychiatric symptoms (Stahl et al. 1997, Zajecka et al. 1997, Rosenbaum et al. 1998). Black and his friends (2000) noted that symptoms of SSRI discontinuation syndrome are quite different from the symptoms occurring following the discontinuation of tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs). Symptoms due to TCA discontinuation usually include five main symptom groups: 1) gastrointestinal and general somatic distress symptoms, e.g. anxiety, agitation, muscle tension, nervousness, flu-like symptoms, nausea, vomiting; 2) sleep disturbances such as insomnia, excessive and vivid dreams; 3) movement disorders, e.g., 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 also includes all these groups except for cardiac arrhythmias (Haddad 1998). SSRI discontinuation syndrome consists three additional symptom clusters not included in TCA discontinuation symptoms. These are 1) problems with balance (dizziness, ataxia, vertigo); 2) sensorial abnormalities (electric shock like sensations, paraesthesia); and 3) aggressive and impulsive behavior (suicide attempts, hoarding). Among these, the most common symptoms noted in several studies were dizziness, nausea/vomiting, headache and lethargy (Haddad 1998, Tamam and Ozpoyraz 2002). Based on these wide range symptom profiles and clinical features, two closely similar diagnostic criteria for SSRI discontinuation syndrome have been proposed (Haddad 1998, Black et al. 2000). Contrary to Black and his friends' (2000) proposal, which has been mentioned in introduction section of this report, Haddad (1998) claimed that the diagnosis of the syndrome required at least two symptoms to appear within 1 to 10 days after discontinuation or reduction in dose of an SSRI after at least 1 month of use. Though provisional at this time and need further testing, these criteria could help the researchers to standardize their discontinuation syndrome diagnosis and arrange their treatment and further studies accordingly.

Despite the differences in the drug used, all cases presented in this article seem to meet the proposed SSRI discontinuation syndrome criteria of Black his friends. Consistent with these criteria, our patients had been taking two different SSRIs between three to four months before the abrupt discontinuation. Our cases experienced the syndrome when stopped their drug intake abruptly. However as stated in proposed criteria (Black et al. 2000), these symptoms could also occur not only after abrupt discontinuation but also during reduction of the prescribed dose.

In the vast majority of patients, SSRI discontinuation symptoms occur within 1 to 3 days after cessation or reduction in dose (Lejoyeux and Ades 1997). Of 42 patients in one study, 82% had onset of withdrawal symptoms within 1 to 3 days and 94% within 1 week; all patients were symptomatic within 2 weeks (Black et al 2000). In a recent study (Bogetto et al. 2002), the mean time at onset of discontinuation symptoms was 2 days after drug discontinuation and mean duration was 5 days. As in prior studies (Coupland et al. 1996, Michelson et al. 2000), SSRI discontinuation syndrome commenced 30 hours to 3 days after the last dose received in our patients. In most cases, the discontinuation syndrome is mild and short-lived, even if untreated (Tamam and Ozpoyraz 2002). Discontinuation symptoms usually resolve within 72 hours after re-initiation of the same SSRI or any other antidepressant with an identical pharmacological profile (Diler and Avci 2002). Symptoms in our cases had immediately resolved when they received the same antidepressant and had recovery within 48 hours after recommencing the drug. The last case had a spontaneous recovery within the 3 days. In a recent meta-analysis of 26 cases of spontaneous resolution (Black et al. 2000), 47.6% of symptoms resolved in less than 1 week, which was quite consistent with our cases; in the remainder of the cases, symptoms lasted longer. In his unique case report, Green (2002) reported five patients who suffered prolonged neurological symptoms (nocturnal twitching, irritability, paraesthesia, myoclonic jerks) for as long as 18 months after discontinuing their medication.

The simplest and mostly supported explanation for SSRI discontinuation syndrome is a relative deficiency of serotonin in synapses and synaptic vesicles (Schaztberg et al. 1997a, 1997b). This deficiency takes different clinical profiles depending on the type of SSRI. There appears to be a meaningful relationship between the plasma half-lives of SSRIs (i.e. 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 (Michelson 2000). 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 (Haddad 1998). Price and his friends (1996) reported that discontinuation symptoms 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 (Rosenbaum et al 1998), the incidence of discontinuation syndrome observed in fluoxetine-treated patients (14%) was significantly lower than the pooled incidence for sertraline- (60%) and paroxetine-treated (66%) patients. Contrary to other SSRIs, studies associated with citalopram discontinuation syndrome are scarce in the literature because of the drug's relatively late availability in the US market. Besides in a recent study, rapid discontinuation of citalopram has been reported to result in mild and transient CNS events, which might be an indicator of discontinuation syndrome (Markowitz et al. 2000).

Cases presented in this article were treated with drugs with relatively shorter half-lives that might highly contribute to occurrence of the discontinuation syndrome. Aside from its shorter half-life and absence of an active metabolite, paroxetine's greater anticholinergic effect, greater potency in blocking serotonin reuptake may also account for higher frequency of discontinuation syndrome with paroxetine (Rosenabum et al. 1998). Though almost all controlled studies approved and reported discontinuation syndrome rate to be highest after cessation of paroxetine among all SSRIs, severity of withdrawal symptoms amongst different SSRIs have not been examined in detail.

Despite these theoretical explanations about pathophysiology of discontinuation syndrome, the pathophysiology and underlying mechanisms for SSRI discontinuation have not yet clearly defined. Further researches to describe these mechanisms are critically needed.

Missing even a dose of an SSRI might lead to discontinuation syndrome, with the exception of fluoxetine (Kaplan 1997). As many patients do not report a missed dose unless they are persistently and directly questioned, the emerging discontinuation symptoms (i.e. anxiety, irritability, fatigue and insomnia) may be interpreted as depressive symptoms and mistaken for a relapse of the depressive episode. Thus, in turn, these may lead to recommencement of a discontinued treatment, an increase in dosage, a change in the drug, or addition of a new drug (Kaplan 1997).

Several strategies have been suggested to manage discontinuation symptoms related with SSRIs (Rosenbaum et al. 1997). First of all, as stated above patients should be told that their symptoms are likely to be short lived and mild; at this point most patients only need reassurance. An educational approach conveying appropriate messages may help them cope with these side effects. Compliance with the treatment has the core role then. Patients should repeatedly be reminded of importance of regular drug intake, as even transient noncompliance can lead to discontinuation symptoms and major role of compliance in avoiding such disturbing symptoms (Rosenbaum et al. 1997). When treatment has been completed all SSRIs should be slowly tapered to the minimum therapeutic dose and then terminated. The rate of tapering should depend on drug's profile, dose, and treatment duration. Sometimes, despite slow tapering, symptoms may still occur, whereupon the original dose should be reinstated and tapering extended for more weeks. If side effects or severe discontinuation symptoms render continuing original drug untenable, substituting fluoxetine, which has an extended half-life for other SSRI's is a rational option to be considered. In our patients, we reinstated the original SSRIs for treatment, which leaded to complete resolution within 48 hours similar to reports in literature (Bogetto et al. 2002, Diler et al 2000).

CONCLUSIONS

All SSRIs and serotonergic drugs can lead to discontinuation syndrome after cessation of the drug or reduction in the dose. Though symptoms comprising SSRI discontinuation syndrome are mostly short lived and mild in nature as in our cases, prompt recognition of these effects is essential to start appropriate management including reintroduction of the drug and a more gradual tapering schedule. As an important contributing factor to non-compliance to the treatment, antidepressant discontinuation syndrome should be borne in mind in detailed assessment of the patients' newly emerging symptoms during treatment with serotonergic agents. The physicians treating such patients, especially general practitioners and specialists other than psychiatrists, should be educated and be alert to prominent features, symptoms and course of this syndrome, which is associated with SSRIs.

REFERENCES

Benazzi F. Mirtazapine withdrawal symptoms. Can J Psychiatry 1998; 43:525.

Black K, Shea C, Dursun S, Kutcher S. Selective serotonin reuptake inhibitor discontinuation syndrome: proposed diagnostic criteria. J Psychiatry Neurosci 2000; 25:255-261.

Bogetto F, Bellino S, Revello RB, Patria L. Discontinuation syndrome in dysthmic patients treated with selective serotonin reuptake inhibitors. CNS Drugs 2002; 16:273-283.

Boyd IW. Venlafaxine withdrawal reactions. Med J Aust

1998; 169:91-92.
Coupland N, Bell CJ, Potokar JP. Serotonin reuptake inhibitor withdrawal. J Clin Psychopharmacol 1996; 16:356-362.
Diler RS, Avci A. Selective serotonin reuptake inhibitor discontinuation syndrome in children: Six case reports. Curr Ther Res Clin Exp 2002; 63:188-197.
Diler RS, Tamam L, Avci A. Withdrawal symptoms associated with paroxetine discontinuation in a 9-year old boy. J Clin Psychopharmacol 2000; 20:586-587.
Green B. Persistent adverse neurological effects following SSRI discontinuation (PANES). Psychiatry On-line. 2002; accessed October 2002 on http://www.priory.com/psych/panes.htm.
Haddad P. The SSRI discontinuation syndrome. J Psychopharmacol 1998; 2:305-313.
Kaplan EM. Antidepressant noncompliance as a factor in the discontinuation symptoms. J Clin Psychiatry 1997; 58 (Suppl 7):31-36.
Lejoyeux M, Ades J. Antidepressant discontinuation: A review of the literature. J Clin Psychiatry 1997; 58 (suppl 7):11-16.
Markowitz JS, DeVane CL, Liston HL, Montgomery SA. An assessment of selective serotonin reuptake inhibitor discontinuation symptoms with citalopram. Int Clin Psychopharmacol 2000; 15:329-333.
Michelson D, Fava M, Amsterdam J, Apter J, Londborg P, Tamura R, et al. Interruption of selective serotonin reuptake inhibitor treatment. Br J Psychiatry 2000; 176:363-368.
Olver JS, Burrows GD, Norman TR. Discontinuation syndromes with selective serotonin reuptake inhibitors. Are there clinically relevant differences? CNS Drugs 1999; 12:171-177.
Price JS, Waller PC, Wood SM, Mackay AV. A comparison of post-marketing safety of four selective re-uptake inhibitors including the investigation of symptoms occurring on withdrawal. Br J Clin Pharmacol 1996; 42:757-763.
Rajagopalan M, Little J. Discontinuation symptoms with nefazodone. Aust NZ J Psychiatry 1999; 33:594-597.
Rosenbaum JF, Fava M, Hoog SL, Ascroft RC, Krebs WB. Selective serotonin reuptake inhibitor discontinuation syndrome: a randomized clinical trial. Biol Psychiatry 1998; 44:77-87.
Rosenbaum JF, Zajecka J. Clinical management of antidepressant discontinuation. J Clin Psychiatry 1997; 58(suppl 7):37-40.
Schatzberg AF, Haddad P, Kaplan EM, Lejoyeux M, Rosenbaum JF, Young AH, et al. Serotonin reuptake inhibitor discontinuation syndrome: A hypothetical definition. J Clin Psychiatry 1997a; 58(suppl 7):5-10.
Schatzberg AF, Haddad P, Kaplan EM, Lejoyeux M, Rosenbaum JF, Young AH et al. Possible biological mechanisms of serotonin reuptake inhibitor discontinuation syndrome. J Clin Psychiatry 1997b; 58(suppl 7):23-27.
Stahl MMS, Lindquist M, Peterson M, Edwards IR, Sanderson JH, Taylor NFA, et al. Withdrawal reactions with selective serotonin re-uptake inhibitors as reported to the WHO system. Eur J Clin Pharmacol 1997; 53:163-169.
Tamam L, Ozpoyraz N. Selective serotonin reuptake inhibitor discontinuation syndrome: A review. Adv Ther 2002; 19:17-26.
Young AH, Currie A. Physician knowledge of antidepressant withdrawal effects: A survey. J Clin Psychiatry 1997; 58(Suppl 7):28-30.
Zajecka J, Tracy KA, Mitchell S. Discontinuation symptoms after treatment with serotonin reuptake inhibitors: A literature review. J Clin Psychiatry 1997; 58:291-297.