

SSRI WITHDRAWAL SYNDROME

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Objective: To present a possible case and review symptoms associated with discontinuation of selective serotonin reuptake inhibitors (SSRIs) and to discuss how these symptoms may be prevented or reduced in intensity.

Data Source: A MEDLINE search from 1982 to May 1997 was performed to identify literature concerning SSRI withdrawal reactions. The references of articles found were evaluated for other relevant articles.

Study Selection: Case reports, letters to the editor, and retrospective reviews, describing symptoms observed after discontinuation of SSRIs.

Data Extraction: Data detailing the symptoms observed after medication discontinuation, factors that predispose individuals to these symptoms, and methods to reduce appearance and/or reduce severity.

Data Synthesis: Withdrawal syndrome is most likely to occur in patients who receive SSRIs with a short half-life. Interestingly, the SSRI with the shortest half-life is also the most pharmacologically selective of the agents available. Withdrawal may occur when the SSRI has been used for a minimum of five weeks. Symptoms occur within one to seven days of discontinuation or taper and usually resolve within weeks or when the SSRI is restarted.

Conclusion: Discontinuation of SSRIs in some cases leads to withdrawal symptoms that may be reduced or prevented by slowly tapering the SSRI.

Key Words: Affective disorders; Depression; Withdrawal syndrome; Discontinuation syndrome.

Abbreviations Used: SSRI = selective serotonin reuptake inhibitors; SSNRI = selective serotonin-norepinephrine reuptake inhibitor; TCA = tricyclic antidepressant; MAOI = Monoamine oxidase inhibitor; 5-HT = serotonin; NE = norepinephrine; TSH = Thyroid stimulating hormone; T₄ = thyroxine; OCD = obsessive-compulsive disorder; CNS = central nervous system.

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Discovery of the effectiveness of selective serotonin reuptake inhibitors (SSRIs) in treating affective disorders was a significant advancement in the field of psychiatry. Clinicians had a new addition to their inventory of medications for treating affective disorders resistant to tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs). Fluoxetine, the first SSRI, was introduced in 1985 and soon became one of the most prescribed medications in history. Today, fluoxetine, paroxetine, sertraline, and fluvoxamine are available. Venlafaxine, a structurally novel agent, is classified as a selective serotonin-norepinephrine reuptake inhibitor (SSNRI).

Withdrawal symptoms were not expected with SSRIs since they do not affect the cholinergic system as do TCAs, in which withdrawal symptoms occur frequently after drug discontinuation.

CASE REPORT

An 85-year-old white female with a long-standing history of bipolar disorder was admitted to the hospital with complaints of increasing dyspnea, productive cough, and fever. Prior to admission the patient's medications included sertraline 50 mg/day, risperidone 1 mg b.i.d., phenytoin 100 mg t.i.d. plus 50 mg at bedtime, conjugated estrogens 0.3 mg/day, levothyroxine 50 mcg/day, and aspirin 325 mg/day. Her medical history was significant for bipolar disorder with psychotic features, adult-onset diabetes mellitus, hypertension, coronary artery disease, hypothyroidism, and tonic-clonic seizures. Despite a long, rocky hospital course, her pneumonia responded to treatment with oxygen supplementation and a full course of antibiotic therapy. During the hospital stay she developed deep vein thrombosis and was initially treated with heparin followed by warfarin therapy. She also developed atrial fibrillation, so digoxin 0.25 mg/day and metoprolol 12.5 mg b.i.d. were added to her medications. The

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patient was transferred to the skilled nursing facility in the hospital. Upon completion of a drug regimen review, it was noted that sertraline was discontinued for a period of 10 days and then resumed. The patient remained on all other previously noted medications, except aspirin. Two days after discontinuation of sertraline, the patient had difficulty with anxiety, moderate depression, intermittent psychomotor agitation and difficulty with word finding (alogia), easy distractibility, confusion, receptive aphasia, decreased processing, and gait disturbances.

DISCUSSION OF CASE

This case is representative of the complex nature of providing pharmaceutical care to elderly patients with multiple disease states and medications. Several factors other than the discontinuation of sertraline should be considered in this patient. These factors include hypothyroidism, hyperthyroidism, hypoglycemia, hyperglycemia, phenytoin toxicity, digoxin toxicity, and embolic phenomenon.

A thyroid stimulating hormone (TSH) level was drawn five days before sertraline was discontinued. It is important to note that phenytoin can decrease both total and free serum thyroxine (T_4) concentrations. However, this is not accompanied by elevation of the TSH value in euthyroid patients.¹ The TSH value was within the normal range, indicating adequate thyroid hormone replacement.

Despite a history of adult-onset diabetes mellitus, glucose values ranged from 76–156 mg/dl (normal 70–110 mg/dl) while sertraline was discontinued. The patient received no medications for the treatment of diabetes. Her diabetes was considered well controlled and an unlikely cause of her symptoms.

A phenytoin level of 12 mcg/ml (normal therapeutic range 10–20 mcg/ml) was drawn during this period. Her albumin level was 2.4 gm/dl (normal 3.5–5.0 gm/dl) reflecting poor oral intake during her bout with pneumonia. Phenytoin is highly protein-bound, primarily to serum albumin. Protein binding may

be reduced with hypoalbuminemia, leading to a higher concentration of unbound or free phenytoin. A free phenytoin level was not attained and an adjustment for the low albumin level was required.² The formula (adjusted concentration = measured total concentration $\div [(0.2 \times \text{albumin}) + 0.1]$) yielded a phenytoin level of approximately 21 mcg/ml. It is difficult to correlate serum levels with signs of toxicity due to individual variation in presentation. Nystagmus is associated with a phenytoin level greater than 20 mcg/ml, ataxia and irritability usually occur with a level that exceeds 30 mcg/ml. A level greater than 40 mcg/ml can induce mental changes, drowsiness, seizures and coma.^{3,4} This patient did not have nystagmus and remained seizure-free. Despite the lack of nystagmus, the patient's symptoms were possibly caused or aggravated by phenytoin toxicity.⁵

The patient's digoxin level was 1.1 ng/ml (normal 0.8–2.0 ng/ml), hence this medication was not thought to contribute to the patient's symptoms.

Given the diagnosis of atrial fibrillation made during her hospitalization, a central nervous system (CNS) event (embolic in origin) could account for the patient's symptoms. The patient's international normalized ratio (INR) and activated partial thromboplastin time (APTT) were subtherapeutic and anticoagulant doses were adjusted upward. A computed tomography (CT) scan performed after sertraline was restarted revealed no abnormalities. The normal CT scan ruled out the possibility of a large infarcted area. Small infarcts (< 2 mm) and infarcts that occur near the skull base may escape detection on a CT scan. Magnetic resonance imaging (MRI), which may detect smaller infarcts, was not performed. Due to inadequate anticoagulation during this period a CNS event could not be ruled out.

The patient had received sertraline for 18 months when it was discontinued for 10 days, and then resumed. She had difficulty with anxiety, moderate depression, intermittent psychomotor agitation and difficulty with

word finding (alogia), easy distractibility, confusion, receptive aphasia, decreased processing, and gait disturbances. The symptoms remitted after resuming sertraline, therefore we considered serotonergic withdrawal syndrome to be the most likely cause of her symptoms. It is possible that phenytoin toxicity and a CNS event were factors that may have caused or contributed to her symptoms. In geriatric patients with multiple diseases and medications, it is often difficult to discern the precise cause of adverse events.

LITERATURE REVIEW

The first report of withdrawal symptoms occurring after SSRI discontinuation was in 1992 with fluvoxamine.⁶ In 1993 the Committee of Safety of Medicines in the United Kingdom reported withdrawal symptoms with paroxetine.⁷ Sertraline withdrawal reports appeared in 1994.⁸ Only a few reports of withdrawal symptoms with fluoxetine have been published.⁹⁻¹¹

In 1995, Dominguez and Goodnick reported on three patients who displayed withdrawal effects within two days after discontinuing paroxetine.¹² Patient number one, a 37-year-old woman, was being treated for major depressive disorder with paroxetine, 40 mg/day for five months. The paroxetine was abruptly stopped and three days later, she reported a feeling of electricity throughout her body, along with vivid dreams, nightmares, tremor, and dizziness. She was restarted on paroxetine at 10 mg/day on the same day and by the second dose, her symptoms had abated.

Patient number two, a 26-year-old woman, was started on paroxetine at 10 mg/day without any improvement in her obsessive-compulsive disorder (OCD). The dosage was increased slowly to 40 mg/day and maintained for 10 weeks. The paroxetine was stopped suddenly due to lack of response and continued GI distress. Two days later, she called to complain of uncontrolled crying spells, dizziness, vivid dreams, depersonalization, increased appetite, and insomnia. She was instructed to restart

paroxetine at 10 mg/day and within two days, her symptoms were gone.

Patient number three, a 48-year-old woman, was treated for OCD with paroxetine at 20 mg/day for six weeks. Her dosage was gradually increased to 40 mg/day due to her partial response. After six months, the paroxetine was discontinued. She presented to the clinic four days later complaining of dizziness, moderate nausea, tiredness, and chills, which she said had started the day before. She also reported some diarrhea, vivid dreams, nightmares, crying spells, and poor concentration. She was restarted the same day on paroxetine, 20 mg/day. She reported that within 24 hours, she felt 90% better. Two days later, she was completely recovered.

Pacheco et al. in 1996 reported five cases of paroxetine withdrawal syndrome in young women.¹³ Each patient was treated for major depression and started on paroxetine at 10 mg/day. The dosage was increased to 20 mg/day after the first week of therapy and maintained there for the duration of their treatment. Three patients had their paroxetine discontinued by a slow taper over four weeks. The other two had tapers from 20 mg to 10 mg for two weeks, then stopped completely.

All patients complained of vertigo, lightheadedness, or gait instability while withdrawing from paroxetine. The symptoms persisted for seven days in each patient. Two patients demanded urgent treatment and were prescribed lorazepam 1 mg/day for one week. No patients received paroxetine to relieve the withdrawal symptoms.

Reeves and Pinkofsky reported a 39-year-old white woman who was treated with paroxetine, 20 mg/day for one year, for major depressive disorder.¹⁴ She ran out of her medication while on vacation and within 30 hours she reported nausea, hot and cold flashes, headache, and lightheadedness. She also described an electric shock that traveled through her back and limbs when she moved. Her symptoms worsened over the next two days and she went to a local emergency room.

She was restarted on paroxetine at 20 mg/day and within four hours, her withdrawal symptoms were relieved.

Fava and Grandi reported a 43-year-old man treated with 40 mg/day of paroxetine for major depressive disorder.¹⁵ After three months of therapy, and only showing a partial response, the paroxetine was reduced to 20 mg/day. Three days later, desipramine was started at 50 mg/day, then increased to 100 mg/day. After seven days of desipramine therapy, the patient complained of severe vertigo, gait instability, malaise, muscle aches, and hypnagogic visual hallucinations. Desipramine was reduced to 25 mg/day for three days, then discontinued. The withdrawal symptoms gradually disappeared over 10 days and desipramine was reinstated. He showed a full response with desipramine at 150 mg/day after four weeks of therapy.

A 22-year-old woman with schizoaffective disorder, depressive type, was treated with haloperidol (3 mg/day) and paroxetine (40 mg/day) without success. Desipramine (50 mg/day) was substituted for the paroxetine without tapering the paroxetine. Ten days later, with her desipramine dosage at 100 mg/day, the patient developed nausea, emesis, myalgia, psychomotor agitation, and middle insomnia. These symptoms disappeared gradually over a week. The desipramine dose was increased to 200 mg/day, and her depressed mood improved.

A 25-year-old woman was treated for major depressive disorder with clomipramine, but it was later discontinued due to bothersome tachycardia. Paroxetine was started at 20 mg/day. She improved and the paroxetine was discontinued after four months of treatment. One week later, she developed fatigue, agitation, rhinorrhea, myalgia, and middle insomnia. These symptoms faded over 10 days.

Three recent reports of withdrawal symptoms with venlafaxine were reported by Louie et al.¹⁶ The first was a 46-year-old white woman treated for chronic major depression with venlafaxine, gradually increased to 112.5

mg/day. Nine weeks later, the dose was reduced to 37.5 mg b.i.d. for 10 days, then 18.75 mg b.i.d. Three days later, she complained of auditory hallucinations, abdominal distention, nausea, chills, fatigue, urinary frequency, and bizarre dreams. Venlafaxine was increased to 56.25 mg/day and her symptoms subsided. When the dose was reduced by 12.5 mg/day every one to two weeks, with the exception of the hallucinations, her symptoms would reappear. Venlafaxine was discontinued 10 weeks after her withdrawal symptoms first appeared.

The second patient, a 37-year-old white man, was treated for 19 weeks with venlafaxine 150 mg/day for major depression. He stopped the medication and within 24 hours experienced nausea, dizziness, a shock-like sensation in his neck when he turned his head, more frequent dreaming, and recurrence of depression. His symptoms disappeared when venlafaxine was restarted. These withdrawal symptoms returned two months later when he missed his dose for 24 hours, but again disappeared when he took his medication.

The third patient was a 37-year-old black man treated for compulsive behavior and dysthymia with venlafaxine 37.5 mg t.i.d. After one month, he abruptly stopped his medication and three days later developed nausea, diarrhea, and dizziness. He resumed his venlafaxine three days later at 37.5 mg b.i.d. and the symptoms stopped.

Berlin reports of three cases of withdrawal symptoms from fluoxetine.⁹ The first patient was a 36-year-old man treated for mixed generalized anxiety, dysthymia, and some obsessional traits with fluoxetine 20 mg/day as adjunct to psychotherapy. Fourteen months later the dose was increased to 40 mg/day due to some situational stress. After one month on this dose, fluoxetine was discontinued without tapering, at the patient's request. Two days later he started experiencing short spells of dizziness and vertigo. The spells only lasted for a few seconds, but occurred numerous times during the day. Ten days after stopping

TABLE 1. BASIC PHARMACOKINETIC PARAMETERS OF SSRIs²⁰

Parameter	Fluvoxamine	Fluoxetine	Paroxetine	Sertraline
GI absorption	> 94%	80%	> 64%	> 44%
T _{max} (Hr)(range) ^a	5(1-8)	6-8	5(0.5-11)	2-4
Bioavailability	53%	94%	100%	NA
Protein binding	77%	95%	95%	99%
Half life parent	15 hours ^b	1.9 days	18-24 hours	26 hours
active metabolite	NA	7-9 days	NA	62 hours ^c
Renal excretion ^d	94%	80%	64%	44%
Fecal excretion ^d	—	15%	36%	44%

^aTime to reach peak plasma concentration^bIncreases by 30%-50% after multiple dosing^cEight times less potent than sertraline^dPercentage of oral dose

fluoxetine, he had a gradual return of his symptoms of self-doubt, irritability, and emotional lability. He remained off medications for 26 days, at which time he restarted fluoxetine 40 mg/day. Two days after restarting fluoxetine, the vertigo and dizziness abated and approximately three weeks later, his emotional lability and irritability also stopped.

He continued on fluoxetine for another 15 months and then again asked to stop the medication, again without tapering. Two days later, the vertigo and dizziness "spells" returned. He remained off fluoxetine for 29 days, during which time the vertigo and dizziness were described as annoying but not disabling. He again restarted fluoxetine 40 mg/day and once again, after three days, the vertigo and dizziness disappeared.

The second patient was a 34-year-old man treated with fluoxetine 20 mg/day and psychotherapy for major depressive episodes and long standing obsessional thoughts. Six weeks of therapy stopped his depression and obsessional thoughts. Fluoxetine was continued for seven months, then the dose was reduced to 20 mg every other day for three months. The medication was then further reduced to 20 mg twice a week for two weeks and then

stopped completely. One week later he complained of "feeling off balance," which lasted for a few seconds and occurred several times daily. These symptoms were somewhat bothersome, made worse by motion, but not debilitating. The symptoms persisted for approximately eight weeks after fluoxetine was discontinued.

The third patient, a 52-year-old man, was treated for major depressive episode with psychotherapy, fluoxetine 20 mg/day and alprazolam p.r.n. (average dose 1.25 mg/day). Nine weeks later, after complete resolution of this depression, both medications were discontinued without tapering. Three and a half weeks later, he reported onset of lightheadedness of short duration, which occurred with sudden head movements. These symptoms gradually disappeared over the next four weeks.

Einbinder described a young woman treated for depression with fluoxetine 20 mg/day.¹⁰ One month later, her dosage was increased to 40 mg/day because she failed to respond. Two months after her dosage was increased, she felt better and her medication was discontinued without tapering. Three days later she felt fatigued and two days later she resumed her fluoxetine 40 mg/day. She

TABLE 2. SUGGESTED SSRI AND SSNRI TAPERING SCHEDULE

Fluoxetine*	Reduce by 5 mg every two weeks until dose is 5 mg/day, then 2.5 mg every two weeks
Fluvoxamine	Reduce by 25 mg every two weeks until dose is 25 mg/day, then 12.5 mg every two weeks
Paroxetine	Reduce by 10 mg every two weeks until dose is 10 mg/day, then 5 mg/day every two weeks
Sertraline	Reduce by 25 mg every two weeks until dose is 25 mg/day, then 12.5 mg every two weeks
Venlafaxine	Reduce by 25 mg every two weeks until dose is 25 mg/day, then 12.5 mg/day every two weeks

*A liquid preparation may be used for the 5 mg and 2.5 mg dose

EXAMPLE CASE: A patient with depression is receiving 20 mg/day of fluoxetine. Upon discontinuation she experiences symptoms of SSRI withdrawal. Resume fluoxetine at a dose of 20 mg/day until symptoms abate. Then decrease the dose by 5 mg to 15 mg/day for two weeks. If the patient tolerates the lower dose without withdrawal symptoms decrease the dose to 10 mg/day for two weeks. Continue the taper according to the above schedule.

continued on the fluoxetine for two months, at which time she again stopped the medication. As before, nine days after stopping the fluoxetine, she complained of extreme dizziness. She also developed an eye twitch 14 days after stopping her medication. All medical exams were negative.

She once again resumed the fluoxetine at 20 mg/day and after three days the symptoms subsided. The fluoxetine was then slowly tapered by 5 mg every two weeks. Five days after the final dose, she had a recurrence of her previous symptoms. She resumed fluoxetine 5 mg/day. Again her symptoms cleared after two days. She stayed at 5 mg/day for two weeks, then dropped to 2.5 mg/day for two weeks, then stopped the medication without further withdrawal effects.

Mallya, White, and Gunderson describe two patients involved in SSRI drug studies.¹⁷ The first woman was 36-years-old with a long history of OCD. She was admitted into the fluvoxamine drug study. At the eleventh week, she was accidentally given another patient's medication (a placebo). She complained of dizziness and headaches throughout the week she received the wrong medication.

The mistake was corrected and she continued on the open-label extension of the study for one year, receiving 100 mg/day of fluvoxamine. At the end of the year, she began tapering the medication at 50 mg per

week. Two days after beginning the taper, she reported dizziness, trouble with memory, confusion, low energy, tingling in her extremities, and weakness. These symptoms continued throughout the taper and gradually decreased over the following seven days.

Another OCD study patient, a 56-year-old woman, took fluvoxamine 200 mg/day for one year in the open-label section. She tapered the fluvoxamine at 100 mg/week. Three days after beginning the taper, she complained of headaches, dizziness, poor appetite, nausea, tightness on her heart and chest, and weakness. When she increased the fluvoxamine, her symptoms cleared.

She was admitted into another SSRI study some time later. After taking 50 mg/day of fluvoxamine for six months, she began a randomized double-blind withdrawal phase where she would either receive a full medication dose or a placebo. Two days into this phase, she experienced the same symptoms as when she tapered from fluvoxamine in the previous study, plus lightheadedness, nightmares, and a "slamming against her head," which she described as "like electricity." She paged the physicians one week later complaining of a worsening of her symptoms, which now included cold hands, night sweats, and intermittent nausea. Her symptoms abated two weeks after beginning the withdrawal phase of the study.

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TABLE 3. SYMPTOMS ASSOCIATED WITH SSRI WITHDRAWAL SYNDROME

- Lightheadedness
- Dizziness
- Vertigo
- Gait instability
- Headaches
- Fatigue
- Insomnia
- Bizarre dreams
- Confusion
- Problems with concentration and memory
- Gastrointestinal distress
- Electric shock sensations
- Anxiety
- Paresthesia
- Irritability

GENERAL DISCUSSION

The cause of withdrawal syndrome following discontinuation of SSRIs is unknown, but the electric shock sensations reported with neck flexion are identical to Lhermitte's sign, which appears with dysfunction of the posterior spinal cord. This suggests change at a neuronal level.¹⁴ It has been proposed that inhibition of reuptake initially increases the synaptic concentration of serotonin. Exposure to high concentrations of 5-HT, even for as short as five weeks, may cause down-regulation of receptors. When the SSRI is discontinued the concentration of 5-HT falls. The lower level of 5-HT is insufficient to provide an adequate agonist stimulus for the down-regulated receptors, resulting in withdrawal syndrome.⁶ Inhibition of 5-HT and norepinephrine receptors may be involved in withdrawal symptoms from venlafaxine.

Paroxetine possesses muscarinic anticholinergic activity and may cause withdrawal symptoms via the same mechanism as the TCAs.¹⁸

Compared to other SSRIs, paroxetine is the most pharmacologically selective antagonist at the 5-HT reuptake site.¹⁹ The withdrawal syndrome usually subsides within several weeks of discontinuation in most reports. We found no data describing patients at highest risk for the phenomenon.

The pharmacokinetic differences among the SSRIs are presented in Table 1.²⁰ Withdrawal syndrome is most likely to occur in patients who receive SSRIs with a short half-life. A long half-life of the parent compound and/or active metabolite leads to a more gradual withdrawal. The onset of symptoms following abrupt discontinuation or taper is within one to seven days.^{21,22}

A tapering regimen is not provided in manufacturers' package inserts. The optimum tapering regimen for each agent has yet to be determined by comparative clinical trials. From a review of the case reports, we suggest the tapering schedules presented in Table 2.

CONCLUSION

From the literature, paroxetine appears to be the SSRI most likely to cause withdrawal syndrome, with fluvoxamine and sertraline a close second, possibly due to their high inhibition constants and their shorter half-lives. Published fluoxetine withdrawal reports are scarce, possibly due to the long half-life of fluoxetine and the active metabolite norfluoxetine. Adequate controlled studies are needed to determine the true incidence of withdrawal syndrome, describe patient risk factors, and design the best regimen for tapering the dose of each SSRI. Considering the relatively few published reports available concerning this syndrome compared to the large number of patients who are prescribed SSRIs, we consider withdrawal syndrome to be an uncommon event. Until studies are completed, we recommend that consultant pharmacists monitor for withdrawal symptoms (Table 3) for a minimum of seven days in all patients who discontinue SSRI therapy. If symptoms occur, advise prescribers to restart the SSRI and slowly taper patients off the medication.