Discontinuation of Antidepressant Therapy: Emerging Complications and Their Relevance

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This section of The Journal of Clinical Psychiatry *summarizes the highlights of a satellite symposium entitled "Discontinuation of Antidepressant Therapy: Emerging Complications and Their Relevance," held April 24, 1997, at the European Congress of the World Psychiatric Association in Geneva, Switzerland.*

Participants were Peter Haddad, M.D., Consultant Psychiatrist, Trafford Hospital, Manchester, U.K.; Nick J. Coupland, M.D., Assistant Professor, Department of Psychiatry and Assistant Director of the Psychopharmacology Unit, University of Alberta, Edmonton, Alberta, Canada; David Michelson, M.D., Clinical Research Physician, Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana; and Jerrold F. Rosenbaum, M.D., Director, Outpatient Psychiatry Division, Massachusetts General Hospital and Associate Professor, Department of Psychiatry, Harvard Medical School, Boston, Massachusetts.

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Antidepressant Discontinuation Reactions

Discontinuation reactions are a group of characteristic physical and psychological symptoms that commence shortly after stopping or, less commonly, after reducing the dose of an antidepressant, stated Peter Haddad, M.D. These symptoms are usually short-lived, may be suppressed by reintroduction of the antidepressant, and are distinct from either relapse or recurrence of the primary psychiatric disorder. An antidepressant discontinuation reaction was first reported in 1959 in association with imipramine,[1] but it is now well established that this phenomenon occurs with most antidepressants.[2]

Dr. Haddad noted that while some authors refer to "*antidepressant withdrawal reactions* or an *antidepressant withdrawal syndrome*, I much prefer the term *discontinuation reaction*. *Withdrawal* implies dependence, and antidepressants are drugs of neither dependence or addiction."

Unfortunately, the majority of the public, at least in Britain, believe that antidepressants are addictive, according to Priest et al.,[3] who reported the results of interviews with over 2000 adults. Seventy-eight percent agreed with the statement, "Antidepressants are addictive." Dr. Haddad emphasized that this misconception should not be fostered.

Discontinuation symptoms are common. In a study of imipramine termination, 55% of patients developed one or more discontinuation symptoms.[4] A similar study with amitriptyline revealed an 80% rate of appearance of these symptoms.[5] In other studies, the incidence was 33% for clomipramine[6] and 32% for phenelzine,[7] and, in a methodologically sound study, the incidence was 35% for paroxetine.[8] The rate of discontinuation symptoms seen with the selective serotonin reuptake inhibitors (SSRIs) varies markedly depending on the specific agent—the incidence is highest for paroxetine and lowest for fluoxetine.

Antidepressant discontinuation reactions have several key clinical features (Table 1). Symptoms generally begin within a few days of stopping treatment. They occur more commonly with longer courses of treatment. In most cases, the symptoms are mild and transient, and resolution usually occurs between 1 day and 3 weeks after onset. However, in some patients, the symptoms can be severe. A final important feature is that these symptoms resolve when the antidepressant is recommenced.

Six main symptom groups have been described following discontinuation of tricyclic antidepressants (TCAs). The first group consists of gastrointestinal (GI) symptoms such as nausea, vomiting, abdominal cramps, and diarrhea. The second group consists of symptoms of general somatic distress such as headaches, lethargy, and sweating (i.e., flu-like symptoms). The third comprises symptoms of sleep disturbance, e.g., insomnia, excessive

Table 1. Clinical Features of Discontinuation Reactions

- Onset within a few days of stopping antidepressant therapy
- Onset unusual > 1 week after termination
- Symptoms usually resolve within 2 weeks
- More common with longer courses of treatment
- Symptoms usually mild
- Symptoms occasionally severe
- Rapid resolution when antidepressant is restarted

Table 2. Symptoms Associated With SSRI Discontinuation

- Gastrointestinal symptoms
- Symptoms of general somatic distress
- Sleep disturbance
- Affective symptoms
- Problems with balance
- Sensory abnormalities

dreaming, and nightmares. The fourth group consists of affective symptoms and includes anxiety, agitation, and low mood. These 4 symptom groups are fairly common with discontinuation of TCAs and are also well recognized with SSRIs (Table 2). The next 2 symptom groups—mania, hypomania, and a variety of movement disorders—are uncommon with TCA termination and even rarer with SSRI discontinuation. Finally, a few cases of cardiac arrhythmias have been reported when tricyclics were suddenly stopped, but no such cases have been reported during SSRI termination.

Two symptom clusters that are well recognized after SSRI discontinuation are problems with balance and sensory abnormalities. Neither group is prominent following TCA termination. Dizziness and light-headedness are the most common symptoms of SSRI discontinuation. Other symptoms of dysequilibrium include vertigo and ataxia. Sensory abnormalities include paresthesia, numbness, and the unusual sensation of electric shocks, particularly in the head, neck, and upper limbs. Dizziness and electric shocks sometimes occur in brief bursts that are precipitated by minor head movements.

Dr. Haddad pointed out that the symptoms are severe in some patients. The increased morbidity in these patients will cause suffering and lead to an impaired quality of life.

If clinicians are unaware of the possibility of an antidepressant discontinuation reaction, they may misdiagnose the symptoms as a relapse of the original psychiatric illness, which may lead to unnecessary reinstatement of long-term antidepressant treatment. Mislabeling an antidepressant discontinuation reaction as a relapse or a recurrence may lead to an incorrect and negative prognosis that has far-reaching social implications. Most symptoms of antidepressant discontinuation are physical rather than psychological. Thus, patients may undergo unnecessary tests in an attempt to elucidate the apparent physical cause.

It is generally known that patients comply poorly with antidepressant treatment and frequently stop taking medication, either deliberately or accidentally, for several days. Discontinuation symptoms may occur when patients miss two doses of the shorter acting antidepressants, and patients who notice a reaction after temporary stoppage of the medication may be reluctant to restart, which could adversely affect the course of depression since standard treatment lasts 6 months.

Case reports illustrate some of the adverse effects of antidepressant discontinuation. One patient missed work because of ataxia,[9] and another made an emergency visit to a psychiatrist[10] after paroxetine discontinuation. Frost and Lal[11] reported a sertraline discontinuation reaction in which severe electric shock-like sensations resulted in difficulty walking and a temporary loss of control of driving, and Rosenstock[12] described a sertraline discontinuation reaction in which dizziness led to a referral to an otolaryngologist. In Britain, the Committee on Safety of Medicines (CSM) conducted a questionnaire survey to investigate the possible impact of paroxetine discontinuation reactions. Over three quarters of respondents indicated the reaction that they spontaneously reported to the CSM was moderate or severe.[13]

Clinicians can help prevent these reactions by tapering antidepressants over 1 month at the end of treatment and by educating patients on the importance of taking medication consistently. Prescriptions should be refilled before running out, and antidepressants should be taken as directed, even on weekends and vacations.

When antidepressant discontinuation reactions occur, Dr. Haddad said, clinicians must be able to recognize and treat them. The characteristic nature of the symptoms and the close temporal relation to antidepressant stoppage aids in recognizing discontinuation reactions. Treatment depends on two factors: (1) whether the antidepressants are still needed and (2) the severity of the symptoms. If antidepressant treatment is still warranted, the patient should resume therapy, and the symptoms will generally resolve within 24 hours. This is the most common outcome for a reaction that follows noncompliance.

However, discontinuation reactions sometimes occur after the physician has stopped treatment, even if the antidepressant dose has been tapered slowly. If the symptoms are mild, as they are for the majority of patients, reassurance might suffice. The patient should be told that these symptoms are well-recognized and likely to gradually become less severe within several days and disappear within 1 to 2 weeks. Symptomatic treatment could be used for severe symptoms. For example, a short course of a benzodiazepine might be prescribed for insomnia.

Restarting the antidepressant and tapering it more slowly is another treatment option.

Discontinuation reactions occur with virtually all antidepressants, Dr. Haddad concluded. Within the SSRI group, the relative risk varies widely, depending on the agent; the incidence is highest for paroxetine and lowest for fluoxetine. Most discontinuation reactions are mild and brief, but occasionally they can be severe. Irrespective of severity, the repercussions may be serious, and clinicians have important roles in prevention, recognition, and treatment of these reactions.

REFERENCES

1. Mann AM, MacPherson AS. Clinical experience with imipramine (G22355) in the treatment of depression. Canadian Psychiatric Association Journal 1959;4:38–47
2. Haddad P. Newer antidepressants and the discontinuation syndrome. J Clin Psychiatry 1997;58(suppl 7):17–22
3. Priest RG, Vize C, Tylee A. Lay people's attitudes to treatment of depression: results of opinion poll for Defeat Depression Campaign just before launch. BMJ 1996;313:858–859
4. Kramer J, Klein DF, Fink M. Withdrawal symptoms following discontinuation of imipramine therapy. Am J Psychiatry 1961;118:549–550
5. Bialos D, Giller E, Jatlow P, et al. Recurrence of depression after discontinuation of amitriptyline. Am J Psychiatry 1982;139:325–329
6. Diamond BI, Borison RL, Katz R, et al. Rebound reactions due to clomipramine. Psychopharmacol Bull 1989;25:209–212
7. Tyrer P. Clinical effects of abrupt withdrawal from tricyclic antidepressants and monoamine oxidase inhibitors after long-term treatment. J Affect Disord 1984;6:1–7
8. Oehrberg S, Christiansen PE, Behnke K, et al. Paroxetine in the treatment of panic disorder: a randomized, double-blind, placebo-controlled study. Br J Psychiatry 1995;167:374–379
9. Keuthen NJ, Cyr P, Ricciardi JA, et al. Medication withdrawal symptoms in obsessive-compulsive disorder patients treated with paroxetine [letter]. J Clin Psychopharmacol 1994;14:206–207
10. Pacheco L, Malo P, Aragues E, et al. More cases of paroxetine withdrawal syndrome [letter]. Br J Psychiatry 1996;169:384
11. Frost L, Lal S. Shock-like sensations after discontinuation of selective reuptake inhibitors [letter]. Am J Psychiatry 1995;152:810
12. Rosenstock HA. Sertraline withdrawal in two brothers: a case report. Int Clin Psychopharmacol 1996;11:58–59
13. Price JS, Walter PC, Wood SM, et al. A comparison of the post-marketing safety of four selective serotonin re-uptake inhibitors including the investigation of symptoms occurring on withdrawal. Br J Clin Pharmacol 1996;42:757–763

Serotonin Reuptake Inhibitor Withdrawal: A Class Effect?

Published case reports of serotonin reuptake inhibitor withdrawal in the literature lead to questions, is there a withdrawal syndrome that affects the class of serotonin reuptake inhibitors, or is the syndrome limited to paroxetine, as some investigators have suggested?

Nick J. Coupland, M.D., described a retrospective case note study he and his colleagues designed to examine the above questions.[1] The researchers used Malcolm Lader's[2] definition: (1) The syndrome should include symptoms that have not been previously experienced as part of the illness. (2) The course should be predictable. (3) The symptoms should be suppressed by reinstituting the original medication.

The investigators examined charts of 171 outpatients for at least 2 weeks after the supervised discontinuation of clomipramine, fluoxetine, fluvoxamine, paroxetine, or sertraline. Because both fluoxetine and sertraline have metabolites that have a longer half-life, the period of investigation for those drugs was extended to 4 weeks after discontinuation.

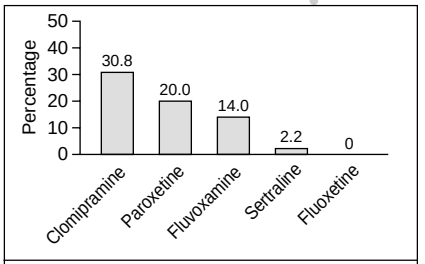
Basic demographic details about each patient were recorded as well as clinical diagnosis, the agent used, the maximum dose, the length of treatment, the rate of taper, and the time to both onset and offset of discontinuation symptoms.

The sample size for clomipramine was 13; for fluoxetine, 20; for fluvoxamine, 43; for paroxetine, 50; and for sertraline, 45. The main finding was that the incidence of discontinuation reactions was higher for clomipramine, paroxetine, and fluvoxamine than for sertraline and fluoxetine (Figure 1).

The most commonly occurring new symptoms were dizziness, paresthesia, and movement-related symptoms. Some patients had visual symptoms, nightmares, or vivid dreams that they had not experienced previously. The median time to onset of symptoms was 3 days, and, in all cases, onset was within a week of drug discontinuation. In a few patients, symptoms began within 24 hours and disappeared within 2 days, but, in the majority of patients, the duration of symptoms was between 14 and 28 days (Figure 2).

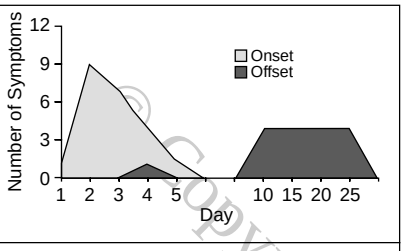
Dizziness was the most frequently reported symptom, particularly in patients who took clomipramine, paroxetine, and fluvoxamine. Some patients described it as a swimming sensation in the head; others, a kind of buzzing or lightheaded feeling. Other people said they felt "spaced out" or drunk. Most patients noted that the symptoms were exacerbated by movement. For example, if a patient suddenly turned his or her head while sitting, a wave of dizziness, which could last for several minutes, might occur. Some patients were unable to work and even were bedridden for a few days until the diz-

Figure 1. Percentage of Patients Who Experience Serotonin Reuptake Inhibitor Discontinuation Symptoms*



*Data from reference 1. No adverse events were reported for fluoxetine.

Figure 2. Course of the Discontinuation Syndrome*



*Data from reference 1.

ziness resolved. The dizziness was often associated with a strange visual symptom—a blurring or jerking of vision or a visual aftertrail—that people had trouble describing.

Paresthesia also occurred frequently, especially after discontinuation of clomipramine, fluvoxamine, and paroxetine. Some patients described feeling a burning or tingling sensation. Others said they felt as if they were experiencing electric shocks or being electrocuted. These sensations were felt most often around the face and neck and upper arms or legs.

When the investigators looked for factors that would predict the risk of discontinuation reactions, they found that discontinuation reactions were more likely in patients who had been treated for at least 2 months, but the risk did not increase further after 6 months of treatment. Most patients in the study were being treated for mood or anxiety disorders, and there was no association between those diagnoses and a discontinuation reaction.

Discontinuation symptoms were sometimes suppressed by reinitiating treatment with either the original agent or another antidepressant with similar pharmacologic properties, said Dr. Coupland. Severe nightmares, insomnia, irritability, and fatigue continued in one clomipramine-treated patient for 5 days, but disappeared within 2 days of initiating venlafaxine treatment. In a published case report, Keuthen et al.[3] found that a paroxetine withdrawal reaction stopped 2 days after the introduction of fluoxetine. In addition, Dr. Coupland noted that he had recently treated a severe paroxetine discontinuation reaction with sertraline, and the physical symptoms resolved within 24 hours.

In conclusion, Dr. Coupland stated that there is evidence that reactions that occur upon discontinuation of serotonin reuptake inhibitors can be termed a syndrome, that this syndrome is associated with chronic, as opposed to short-term, treatment, and that the clinical diagnosis does not predict the risk for experiencing the syndrome. In addition, the risk for a discontinuation syndrome appears to be highest for fluvoxamine and paroxetine, the SSRIs with the shortest half-lives.

REFERENCES

1. Coupland NJ, Bell CJ, Potokar JP. Serotonin reuptake inhibitor withdrawal. J Clin Psychopharmacol 1996;16:356–362
2. Lader M. Benzodiazepine withdrawal states. In: Trimble MR, ed. Benzodiazepines Divided. New York, NY: John Wiley & Sons; 1983:17–31
3. Keuthen NJ, Cyr P, Ricciardi JA, et al. Medication withdrawal symptoms in obsessive-compulsive disorder patients treated with paroxetine [letter]. J Clin Psychopharmacol 1994;14:206–207

Abrupt Discontinuation of Fluoxetine: A Randomized, Placebo-Controlled Study

After abrupt discontinuation, SSRIs are often associated with discontinuation reactions. David Michelson, M.D., and colleagues hypothesized that the long half-life of fluoxetine would protect against these symptoms. To test that hypothesis, they investigated the effects of fluoxetine discontinuation over 6 weeks in 395 patients who were participating in a relapse prevention trial.[1]

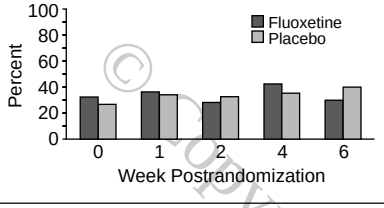
Dr. Michelson pointed out that many previous studies are limited by being retrospective or case reports rather than placebo-controlled, double-blind studies. Until recently, the primary data collection has not been systematized, nor have the adverse events been uniformly classified. In addition, the duration of observation has been limited, which could be relevant for fluoxetine, which has an extended half-life. In fact, the argument has been made that the discontinuation symptoms are delayed, rather than avoided, in fluoxetine.

The 395 patients in the study were fluoxetine responders (Hamilton Rating Scale for Depression score, ≤ 7) who had received 12 to 14 weeks of treatment with 20 mg/day. They were randomly assigned to either continue treatment (N = 299) or receive placebo (N = 96) for an additional 6 weeks. Demographically, these groups were similar in terms of age, gender, duration of depression, and severity of depression.

For those in the placebo group, treatment was abruptly stopped. Spontaneous reports of discontinuation-emergent adverse events were systematically collected at scheduled visits 1, 2, 4, and 6 weeks after discontinuation by trained raters who used a standardized dictionary of adverse event terms. Severity of each event was rated 1 (mild), 2 (moderate), or 3 (severe).

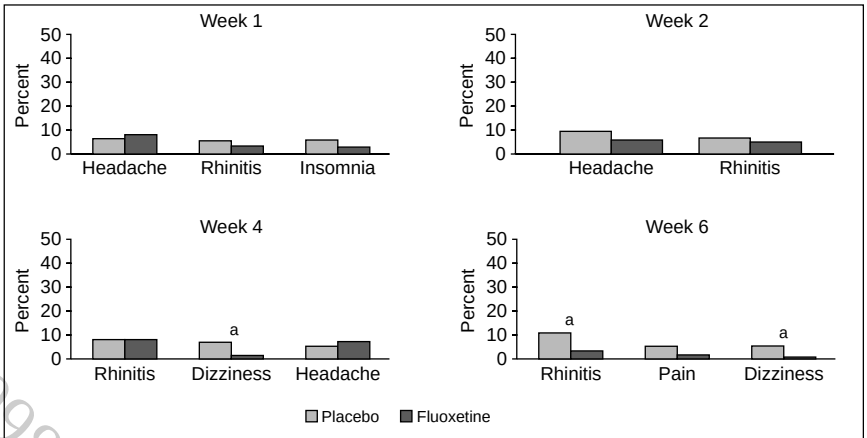
Reports of new or worsened adverse events prior to randomization and after discontinuation were similar for both groups (Figure 3), as was the number of patient discontinuations due to adverse events. There were no statistically significant differences between the fluoxetine and placebo-treated groups during the first 2 weeks postdiscontinuation (Figure 4). At weeks 4 and 6, slightly more placebo-treated patients reported dizziness;

Figure 3. Percentage of Patients Reporting ≥ 1 New or Worsened Adverse Event*



*Data from reference 1. After 12 to 14 weeks of treatment with 20 mg/day of fluoxetine, patients were randomly assigned to continue fluoxetine treatment (N = 299) or abruptly stop fluoxetine treatment (N = 96).

Figure 4. Most Frequently Reported (≥ 5% of Placebo-Treated Patients) New or Worsened Adverse Events*



*Data from reference 1. Patients randomly assigned to continued fluoxetine treatment or placebo treatment.
[a]p ≤ .05.

however, most of these patients had reported dizziness at some point before treatment was stopped, and it was generally classified as mild. Other events that were more common in the placebo group during 1 visit only included somnolence at week 2 and rhinitis and dysmenorrhea at week 6.

These results provide evidence from a prospective, controlled study that abrupt discontinuation of fluoxetine lacks clinically significant sequelae. Mild self-limited light-headedness or dizziness occurred in a small percentage of patients, but the relationship of the symptom, which had little clinical significance, to discontinuation of treatment was uncertain. Symptoms that were statistically significantly more frequent in the placebo group were mild and were reported at 1 visit only in small numbers of patients. They may have been chance variations and seem unlikely to be part of a clinically significant withdrawal syndrome.

In conclusion, said Dr. Michelson, fluoxetine appears to lack clinically significant worsened or new symptoms in the 6 weeks after discontinuation. He attributed this lack of symptoms to the extended half-life of fluoxetine. A growing body of evidence suggests that there are differences in the number and severity of discontinuation events between fluoxetine and the SSRIs that have shorter half-lives.

REFERENCE

1. Zajecka J, Fawcett J, Amsterdam J, et al. Safety of abrupt discontinuation of fluoxetine: a randomized, placebo-controlled study. J Clin Psychopharmacol 1998;18:193–197

Risk of Adverse Events and Depressive Symptom Breakthrough Following Brief Interruption of SSRI Therapy

Jerrold F. Rosenbaum, M.D., described 2 recent studies of antidepressant discontinuation. One study[1] compared taper versus abrupt discontinuation of extended release (XR) venlafaxine, and one study[2] examined the occurrence of adverse events and changes of severity of depressive symptoms when patients experience a 5- to 8-day interruption of treatment with fluoxetine, paroxetine, or sertraline.

Half-life is postulated to be important in determining which agents are most likely to cause a discontinuation syndrome. Venlafaxine has an extremely short half-life of 5 hours as opposed to 21 hours for paroxetine, 26 hours for sertraline, and up to 144 hours for fluoxetine. Once steady state is achieved for drugs with an extended half-life, plasma concentration is less likely to be affected by occasional missed doses and the likelihood for discontinuation events is decreased. Agents with shorter half-lives require less time to wash out of the system before another agent is introduced and are more likely to cause discontinuation symptoms.

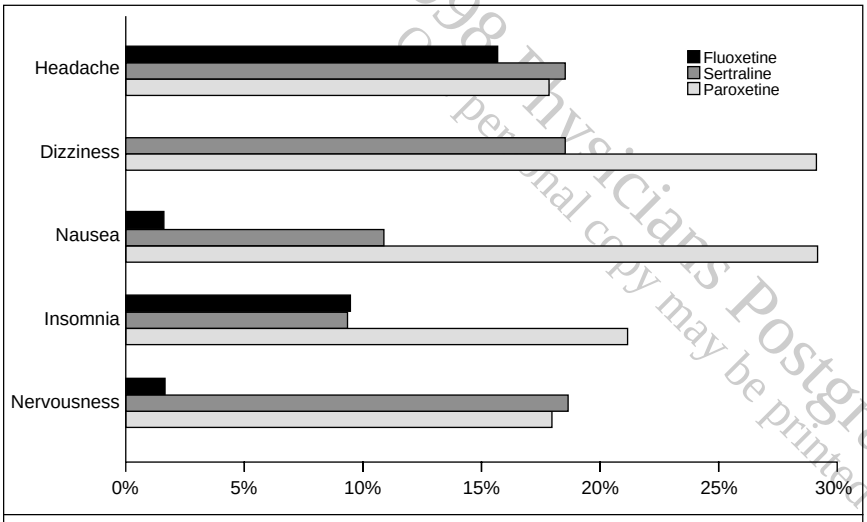
Clinical observations led the researchers to hypothesize that withdrawal symptoms would be common after venlafaxine discontinuation since discontinuation symptoms had been observed after downward titration.

Table 3. Mean Change After Interruption of Fluoxetine, Sertraline, or Paroxetine*

	Fluoxetine (N = 64)		Sertraline (N = 65)		Paroxetine (N = 62)	
Measure	Mean	SD	Mean	SD	Mean	SD
Number of DESS events	0.1[a]	0.9	5.7[b]	0.85	7.2[b]	0.93
SQ somatic symptom subscale score	0.0[a]	2.27	1.2[b]	2.98	2.5[b]	3.77
HAM-D_{28} score	–0.1[a]	5.22	3.4[b]	6.66	5.6[b]	9.12
MADRS score	0.3[a]	6.08	3.5[b]	6.96	7.3[b]	10.48

*Data from reference 2. Abbreviations: DESS = discontinuation-emergent signs and symptoms; HAM-D_{28} = 28-item Hamilton Rating Scale for Depression; MADRS = Montgomery-Asberg Depression Rating Scale; SQ = Symptom Questionnaire.
[a]$p > .5$.
[b]$p < .01$.

Figure 5. Commonly Reported Symptoms After Interruption of Fluoxetine, Sertraline, or Paroxetine*



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At the end of a double-blind, placebo-controlled, multisite study, the investigators[1] compared the rate of the emergence of adverse events in patients with major depressive disorder who stopped treatment with venlafaxine-XR or placebo. Venlafaxine-XR was stopped abruptly after 8 weeks in patients who took 75 mg/day of venlafaxine and tapered over 1 to 2 weeks to 75 mg/day prior to abrupt discontinuation in those who were taking higher doses.

During 3 days after drug discontinuation, 7 (78%) of 9 patients treated with venlafaxine-XR versus 2 (22%) of 9 placebo-treated patients reported the emergence of adverse events so the increase in discontinuation-related adverse events was roughly fourfold, said Dr. Rosenbaum. The most common events were similar to those reported for the SSRIs—dizziness or lightheadedness, irritability, dysphoria, and insomnia. In addition, some patients reported sweating, which may reflect noradrenergic effects.

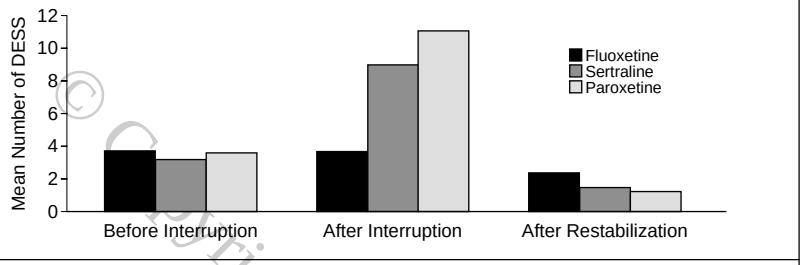
The venlafaxine prescribing information suggests gradual taper in patients taking more than 75 mg/day, and Dr. Rosenbaum suggested that the agent be tapered in all patients.

Discontinuation symptoms often occur when patients either deliberately or accidentally miss several antidepressant doses. Dr. Rosenbaum and colleagues[2] investigated the effects of this intermittent noncompliance in the first gold-standard, double-blind, placebo-controlled, parallel-design study comparing the effects of treatment interruption among SSRIs. Patients with depression had been stabilized during 4 to 24 months of treatment with fluoxetine (20, 40, or 60 mg/day), sertraline (50, 100, or 150 mg/day), or paroxetine (20, 40, or 60 mg/day). Many of the patients had been drawn from general practice and were taking relatively low antidepressant doses (20 mg/day of fluoxetine or paroxetine or 50 or 100 mg/day of sertraline). The samples were demographically comparable at baseline except that the paroxetine- and sertraline-treated groups contained more women than the fluoxetine-treated group.

The 4-week study included two periods of double-blind interruption of treatment, and 191 patients received placebo substitution for 5 to 8 days at either week 2 or week 3. Active drug therapy was resumed, and patients were followed for an additional 1 to 2 weeks. The Discontinuation-Emergent Signs and Symptoms (DESS) checklist and the Symptom Questionnaire were used to assess discontinuation symptoms, and the Montgomery-Asberg Depression Rating Scale (MADRS) and the 28-item Hamilton Rating Scale for Depression (HAM-D_{28}) were used to assess changes in the severity of depressive symptoms (Table 3).

After the interruption of paroxetine treatment, the mean number of DESS jumped from 4 at baseline to 12 (Figure 5). The number of symptoms decreased when treatment was resumed. The results were similar for sertraline, but the response to fluoxetine discontinuation was flat. The differences between fluoxetine and sertraline and flu-

Figure 6. Mean Number of Discontinuation Emergent Signs and Symptoms (DESS)*



*Data from reference 2.

Figure 7. Mean Score on the 28-Item Hamilton Rating Scale for Depression After Interruption of Fluoxetine, Sertraline, or Paroxetine*

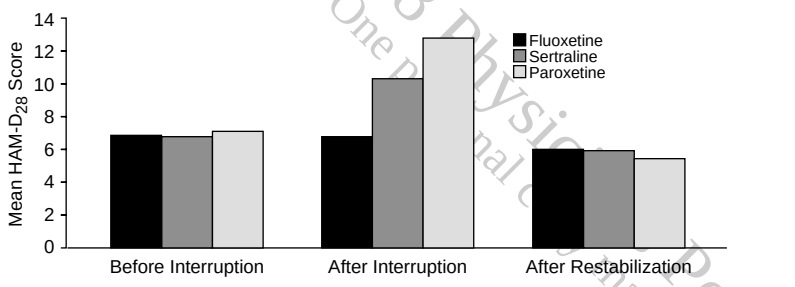


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Table 4. Change in HAM-D_{28} Score After Interruption of Fluoxetine, Sertraline, or Paroxetine*

Score Increase	Fluoxetine (N = 63)	Sertraline (N = 63)	Paroxetine (N = 59)
≥ 8	4 (6%)	19 (30%)	21 (36%)
≥ 10	2 (3%)	12 (19%)	16 (27%)
≥ 12	1 (2%)	9 (14%)	12 (20%)

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oxetine and paroxetine were highly statistically significant ($p < .001$).

Headache, dizziness, nausea, insomnia, and nervousness were commonly reported and were similar to the combination of psychological and flulike symptoms observed in many of the published reports of the discontinuation syndrome (Figure 6). When paroxetine and sertraline were compared with fluoxetine, the rates of irritability, mood changes, agitation, nervousness, and fatigue were increased. Nausea and dizziness appear to be hallmarks of this syndrome.

The investigators also examined whether patients are likely to experience an affective relapse when treatment is interrupted. If depressive relapse is defined as an 8-point or more increase on the HAM-D and a total HAM-D score ≥ 16, 27% of the paroxetine-treated patients, 17% of the sertraline-treated patients, and 2% of the fluoxetine-treated patients had a relapse (Figure 7, Table 4). Scores on the MADRS were similar.

Data show that discontinuation symptoms are clinically significant, and agents with shorter half-lives require increased vigilance when they are interrupted or stopped, Dr. Rosenbaum stated. He suggested treating the discontinuation symptoms by reintroducing the original agent and slowing the rate of taper or by switching to a longer-acting agent, which is essentially self-tapering.

REFERENCES

1. Fava M, Mulroy R, Alpert J, et al. Emergence of adverse events following discontinuation with extended-release venlafaxine. Am J Psychiatry 1997;154:1760–1762
2. Rosenbaum JF, Fava M, Hoog SL, et al. Selective serotonin reuptake inhibitor syndrome: a randomized clinical trial. Biol Psychiatry 1998;44:77–87

Discussion

Participant: Studies of the discontinuation syndrome have involved patients who have been treated with fluoxetine for several months. In patients who have been treated with fluoxetine for several years, is it possible that a chronic dysfunction of serotonin regulation occurs with a secondary inability for fluoxetine withdrawal without relapse?

Dr. Michelson: Unlikely, since there are no apparent differences among patients treated as little as 4 months or as long as 3 years. Eventually, the serotonin regulators adapt, and the amount of available serotonin stabilizes. The liability for experiencing the discontinuation syndrome with most antidepressants, including fluoxetine, doesn't change over time.

Dr. Thompson: In clinical practice, how can we differentiate between changes in mood, irritability, or anxiety as symptoms of discontinuation as opposed to the illness that was treated?

Dr. Coupland: Unlike the symptoms of relapse, discontinuation symptoms, including mood symptoms, disappear within 10 to 28 days (see Figure 2), which is one potential indicator how the discontinuation syndrome might differ from a relapse of illness.

If the symptoms are disabling, treat them by restoring treatment and slow-

ing the rate of taper or substituting a similar agent with a longer half-life.

Dr. Rosenbaum: Reassurance and time are often sufficient treatment for mild discontinuation symptoms.

Dr. Thompson: Citalopram is a potent serotonin reuptake inhibitor with a relatively short half-life that was recently released. Are there data on discontinuation symptoms from this agent?

Dr. Haddad: The Committee for Safety of Medicines in the United Kingdom has received several reports of citalopram discontinuation symptoms.

Dr. Thompson: Dr. Haddad, what is the relationship between the mechanism of action of antidepressants and discontinuation reactions?

Dr. Haddad: These reactions are unlikely until after about 5 weeks of antidepressant treatment, which means the CNS needs to be primed. Presumably, after several weeks of antidepressant treatment, adaptive CNS changes occur and a new homeostasis is established. When antidepressant treatment is stopped, the system needs to readapt. If the antidepressant is stopped suddenly, CNS adjustment cannot keep pace, and discontinuation symptoms will occur. The extended half-life of fluoxetine allows gradual adaptation by the CNS, which is apparently why discontinuation symptoms are unlikely with fluoxetine.

Dr. Thompson: If serotonergic mechanisms are important in discontinuation, how can you explain the high rates of discontinuation syndromes with tricyclic antidepressants (TCAs), some of which have relatively low potency at serotonin reuptake sites?

Dr. Coupland: Discontinuation symptoms are not necessarily an exclusively serotonergic problem. Anticholinergic rebound is well established for the TCAs. Symptoms of TCA withdrawal can often be ameliorated with a cholinergic antagonist. There may not be a unique mechanism for all antidepressant discontinuation—the mechanism of action may vary among classes of antidepressants.

Dr. Thompson: Over what length of time should an antidepressant be tapered?

Dr. Coupland: Most of the patients in our study who discontinued paroxetine treatment on a planned basis were tapered by 10 mg/week.

Dr. Haddad: There's tremendous individual variability among patients. If you look at the case-report literature,[1–2] extremely conservative and gradual tapers have sometimes been necessary, especially for paroxetine. To minimize discontinuation symptoms, taper has sometimes extended over 2 months or more. On the other hand, some patients stop antidepressants abruptly without problems. The individual circumstances of each patient must be considered, but as a general rule, antidepressants that have been administered continuously for 8 weeks or more should be tapered over 4 weeks. This is consistent with advice given in the British National Formulary.[3]

REFERENCES

1. Koopowitz LF, Beck M. Paroxetine-induced withdrawal effects. Hum Psychopharmacol 1995;10:147–148
2. Frost L, Lal S. Shock-like sensations after discontinuation of selective serotonin reuptake inhibitors [letter]. Am J Psychiatry 1995;152:810
3. British National Formulary, Section 4.3, Antidepressant drugs: withdrawal. London: BMA and Pharmaceutical Press; 1998

Conclusion

Discontinuation syndrome is an unjustly neglected phenomenon in antidepressant pharmacotherapy, said Chris Thompson, M.D. He noted that up to 50% of patients, particularly those who are treated in primary care, have unplanned discontinuations from antidepressants. They are noncompliant with their antidepressant treatment without informing their physician. These patients are exposing themselves to the risk of discontinuation reactions. Unfortunately, we lack a method for predicting which patients will be among the majority who will have a relatively mild discontinuation response and which will comprise the few who will have a moderate-to-severe discontinuation response.

When SSRI treatment is interrupted for relatively brief periods, such as 5 to 8 days, discontinuation reactions are more likely and more severe with the agents with short half-lives, paroxetine and sertraline, than with the agent with an extended half-life, fluoxetine. Even when the observation period is extended to 6 weeks, it's difficult to find clearly identifiable discontinuation symptoms with fluoxetine.

Finally, he stated, antidepressant discontinuation has a recognizable syndromal pattern. It's more common with short half-life and sedative drugs, and it can be ameliorated by treatment with fluoxetine or by very slow tapering of the antidepressant dose.

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