

# Newer Antidepressants and the Discontinuation Syndrome

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Data on discontinuation phenomena associated with serotonin selective reuptake inhibitors (SSRIs) are derived primarily from (1) published case reports, (2) data bases of adverse drug reactions that have been spontaneously reported to national monitoring bureaus, and (3) clinical studies of drug discontinuation. Some of the symptoms seen on SSRI discontinuation, such as nausea, lethargy, insomnia, and headache, are similar to those reported with tricyclic discontinuation. However, SSRI discontinuation is also associated with novel symptom clusters, including problems with balance, sensory abnormalities, and possibly aggressive and impulsive behavior. Although generally mild and short-lived, discontinuation symptoms can be severe and chronic and have a major impact on the patient's lifestyle. The incidence of discontinuation symptoms varies widely among the different SSRIs; the highest rate is seen with paroxetine. The variation in incidence might be explained by the different pharmacokinetic and pharmacodynamic profiles of the SSRIs.

*(J Clin Psychiatry 1997;58[suppl 7]:17-22)*

In 1959, Mann and MacPherson<sup>1</sup> described an emergent discontinuation reaction for imipramine. Since then, the existence of discontinuation symptoms for both the tricyclic antidepressants and the monoamine oxidase inhibitors has become well established, particularly through the work of Dilsaver and colleagues.<sup>2-8</sup> Recently, a growing number of discontinuation reactions have been described for the new generation of antidepressants, including the serotonin selective reuptake inhibitors (SSRIs), the tetracyclic antidepressant trazodone, and the serotonin norepinephrine reuptake inhibitor (SNRI) venlafaxine. This paper concentrates on SSRI discontinuation reactions, although venlafaxine discontinuation reactions are also briefly reviewed.

Discontinuation reactions have been reported for all five SSRIs in clinical use today, i.e., citalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline. Although no double-blind studies comparing discontinuation from different SSRIs have been published, data on the relative incidence of discontinuation symptoms are available from anecdotal case reports, data bases of adverse drug reactions that have been spontaneously reported to national monitoring bureaus, and clinical studies.

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*From Prestwich Hospital, Manchester, United Kingdom. Presented at the closed symposium "SSRI Discontinuation Events" held December 17, 1996, in Phoenix, Ariz., and sponsored by an unrestricted educational grant from Eli Lilly and Company.*

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## INCIDENCE

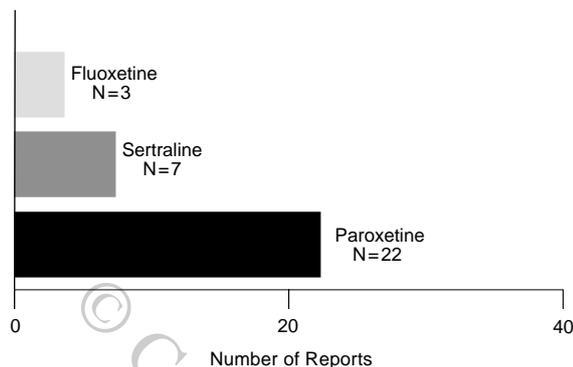
### Anecdotal Case Reports

A comprehensive search of the world literature published up to October 1996 was conducted by the author by using MEDLINE and PSYCHLIT data bases, which were supplemented by the results of a manual search. Forty-seven case reports of SSRI discontinuation reactions, most occurring in the United States, were identified. These detailed clinical vignettes probably represent the severe end of a spectrum of discontinuation reactions. Thirty—over half—published case reports involved paroxetine, while only 7 involved fluoxetine. In both the United States and the United Kingdom, fluoxetine was licensed as an antidepressant before paroxetine, and each year since its introduction, fluoxetine has been prescribed to significantly more patients. Considered against this background, the excess of reports for paroxetine is particularly striking and suggests that discontinuation reactions occur more frequently with paroxetine than fluoxetine. Within the case report literature, several authors have reported more than one case of SSRI discontinuation phenomena, implying that the reactions cannot be rare. For example, Pacheco et al.<sup>9</sup> described five young women who experienced vertigo, light-headedness, or gait instability during tapered withdrawal from paroxetine.

### Adverse Drug Reaction Data

Analysis of data bases of spontaneously reported adverse drug reactions in both the United Kingdom and Australia have also found an excess of reports of discontinuation reactions with paroxetine compared with other

**Figure 1. Number of Spontaneous Reports of Discontinuation Reactions with Serotonin Selective Reuptake Inhibitors.\***



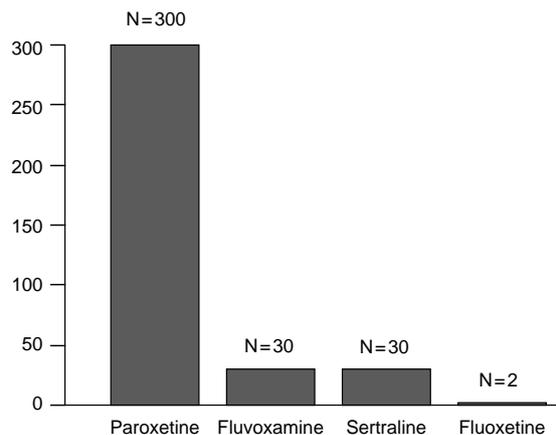
\*Data from reference 11.

SSRIs. In 1993, the United Kingdom Committee on Safety of Medicines (CSM)<sup>10</sup> stated that discontinuation symptoms were more commonly reported with paroxetine than with other SSRIs. While the Committee did not provide comparison figures, it documented 78 reports of paroxetine discontinuation. More recently, the Australian Adverse Drug Reactions Advisory Committee<sup>11</sup> reported that it had received 22 reports of discontinuation reactions for paroxetine, 7 for sertraline, and 3 for fluoxetine (Figure 1). Once again, the excess of reports for paroxetine is particularly striking as it accounts for less than half of the total SSRI prescriptions issued in both the United Kingdom and Australia.

Taking into account the proportions of prescriptions that are written for each SSRI is necessary to obtain an accurate estimate of relative incidence. Price et al.<sup>12</sup> calculated the number of discontinuation reactions per thousand prescriptions for each SSRI on the basis of reports of discontinuation events that were spontaneously lodged by physicians with the Committee on Safety of Medicines in the United Kingdom. The authors estimated an incidence of 300 reports of discontinuation reactions per million paroxetine prescriptions, 30 per million sertraline or fluvoxamine prescriptions, and 2 per million fluoxetine prescriptions (Figure 2).

It is likely that spontaneously reported adverse drug reaction data seriously underestimate the true incidence of SSRI discontinuation reactions. There are several reasons for this. Most discontinuation reactions are mild and presumably go unreported because patients fail to notify their physicians. If a patient does consult, the physician may fail to recognize the nature of the discontinuation symptoms and incorrectly attribute them to either a physical illness, such as the flu, or to a depressive relapse. Gillespie and colleagues<sup>13</sup> surveyed 200 psychiatrists of different nationalities and found that approximately half were unaware that SSRIs were associated with discontinuation phenomena. Even if a discontinuation syndrome is recog-

**Figure 2. Number of Reports of Discontinuation Reactions per Million Prescriptions.\***



\*Data from reference 12.

nized, the physician may not inform the relevant monitoring agency. In the Gillespie et al. survey, only a minority of respondents stated that they would report a discontinuation reaction that they recognized to either a national surveillance unit or a journal.

### Clinical Studies

Clinical studies are the third source of data about discontinuation reactions. In assessing these data, a distinction should be drawn between (1) clinical trial data bases held by pharmaceutical companies, which generally indicate that discontinuation reactions are extremely rare, and (2) clinical studies specifically designed to investigate discontinuation reactions, which consistently find that such reactions are common. The paucity of reports in clinical trial data bases is probably due to several factors. First, discontinuation reactions rarely occur in patients who have received fewer than 8 weeks of treatment with an SSRI, yet clinical trials are often shorter than this. Second, clinical trials seldom include follow-up data after drug cessation. Those that do incorporate follow-up measures usually assess patients for a depressive relapse several months after drug discontinuation. By then, any discontinuation symptoms are likely to have resolved long ago. Finally, it is probable that discontinuation symptoms are more common following cessation of high doses of SSRIs, but clinical trials often use relatively low doses.

Studies specifically designed to assess discontinuation symptoms consistently report high rates. To date, seven such studies have been published (Table 1).<sup>14-20</sup> Although all have methodological weaknesses, they all report clinically significant rates (i.e., 20% and upward) of discontinuation symptoms, at least for some SSRIs. The highest reported rate was 86% of patients stopping fluvoxamine in an open label study.<sup>16</sup> Of particular note are the study by Coupland et al.<sup>17</sup> and that by Oehrberg et al.<sup>20</sup>

**Table 1. Studies of SSRI Discontinuation Reactions**

Study	Drug Withdrawn	N	Withdrawal Symptoms	
			N	%
Black et al. <sup>16</sup> (1993)	Fluvoxamine	14	12	86
Mallya et al. <sup>19</sup> (1993)	Fluvoxamine	17	4	24
Barr et al. <sup>14</sup> (1994)	Paroxetine	6	3	50
Keuthen et al. <sup>18</sup> (1994)	Paroxetine	13	5	39
Oehrberg et al. <sup>20</sup> (1995)	Paroxetine	55	19	35
	Placebo	52	7	14
Bhaumik & Wildgust <sup>15</sup> (1996)	Paroxetine	12	5	42
	Fluoxetine	?	0	0
Coupland et al. <sup>17</sup> (1996)	Clomipramine	13	4	31
	Paroxetine	50	10	20
	Fluvoxamine	43	6	14
	Sertraline	45	1	2
	Fluoxetine	20	0	0

Coupland et al.<sup>17</sup> retrospectively examined case notes to determine the incidence of discontinuation reactions in patients stopping clomipramine and four different SSRIs. They found that the incidence of discontinuation symptoms was significantly higher in patients who had been treated either with clomipramine (31%) or one of the shorter half-life SSRIs, fluvoxamine (14%) or paroxetine (20%), than in patients who had taken one of the longer half-life SSRIs, sertraline (2%) or fluoxetine (0%). In the double-blind, placebo-controlled study by Oehrberg et al.,<sup>20</sup> a 12-week treatment period with either paroxetine or placebo was followed by a 2-week placebo period during which all new symptoms were analyzed. During the final 2-week period, discontinuation symptoms developed in 19 (35%) of the paroxetine-treated subjects as opposed to 7 (14%) of the placebo-treated subjects.

The one published report of citalopram discontinuation involved only two patients<sup>21</sup>; this may indicate citalopram's low relative risk, the agent's limited use to date, or a combination of the two. Among the other four SSRIs, the general consensus from case report data, spontaneous adverse drug reaction data, and clinical studies is that the incidence of discontinuation symptoms is highest for paroxetine, lowest for fluoxetine, and intermediate for fluvoxamine and sertraline. Discontinuation reactions are not unique to SSRIs. The incidence of symptoms seen in studies of paroxetine discontinuation is comparable to that seen in studies of discontinuation of tricyclic antidepressants<sup>22-24</sup> or monoamine oxidase inhibitors,<sup>25</sup> while the incidence with fluoxetine is far lower. Thus, depending on the SSRI chosen, the incidence of discontinuation reactions appears no higher than that seen with older antidepressants and may be far lower.

### **SYMPTOMS OF SSRI DISCONTINUATION**

A great variety of SSRI discontinuation symptoms have been reported. For example, 51 different symptoms were noted in the report of the Australian Adverse Drug Reac-

**Table 2. Discontinuation Syndrome Symptom Profile: SSRIs vs. Tricyclic Antidepressants\***

Symptoms of tricyclic discontinuation <sup>a</sup>	
•	gastrointestinal and general somatic distress (e.g., lethargy, nausea, headache) often with anxiety or agitation
•	sleep disturbances (e.g., insomnia, excessive dreams)
•	movement disorders (akathisia, parkinsonism)
•	behavioral activation (continuum extending to mania)
•	miscellaneous (e.g., cardiac arrhythmias)
Novel symptoms of SSRI discontinuation	
•	problems with balance (e.g., dizziness, ataxia, vertigo)
•	sensory abnormalities (e.g., shock-like sensations, paresthesia, numbness)
•	aggressive and impulsive behavior (e.g., suicidal and homicidal thoughts, shoplifting)
*Abbreviation: SSRI = serotonin selective reuptake inhibitor.	
<sup>a</sup> as classified by Dilsaver et al. <sup>2</sup>	

tions Advisory Committee,<sup>11</sup> 19 symptoms in the study of fluvoxamine discontinuation by Black et al.,<sup>16</sup> and 10 symptoms in the study by Coupland et al.<sup>17</sup> Despite this variation, certain symptoms are consistently reported with a relatively high frequency. These can be regarded as the core symptoms of SSRI discontinuation. The four commonest symptoms, in decreasing order of frequency, appear to be dizziness, nausea, lethargy, and headache. Other common symptoms include anxiety, paresthesia, confusion, tremor, sweating, insomnia, irritability, memory problems, and anorexia (see "Serotonin Reuptake Inhibitor Discontinuation Syndrome: A Hypothetical Definition" in this supplement for further discussion of the symptoms of SSRI discontinuation).

Dilsaver and colleagues<sup>2</sup> divided symptoms of tricyclic antidepressant discontinuation into five main groups: (1) gastrointestinal and general somatic distress symptoms (e.g., lethargy, nausea, headache) often associated with anxiety or agitation; (2) sleep disturbance (e.g., insomnia, excessive dreaming); (3) movement disorders (particularly akathisia and parkinsonism); (4) behavioral activation on a continuum to mania; and (5) miscellaneous symptoms (e.g., cardiac arrhythmias). With the exception of cardiac arrhythmias, these symptom groups have also been described during SSRI discontinuation, though in the category of movement disorder, the SSRI literature is limited to a single published case of an acute dystonic reaction.<sup>26</sup>

Several novel symptoms or symptom clusters, which do not fall within the Dilsaver et al.<sup>2</sup> classification system, are apparent within the literature on SSRI discontinuation, which suggests that the symptoms of SSRI discontinuation may be more varied than those seen with the tricyclic antidepressants (Table 2). These include problems with balance, sensory abnormalities, and possibly aggressive and impulsive behavior.

Problems with balance, which include dizziness, ataxia, and vertigo, have been reported on discontinuation of fluvoxamine, fluoxetine, sertraline and paroxetine. Several reports, including Coupland et al.,<sup>17</sup> state that these

symptoms are sometimes exacerbated by slight movement. Occasionally, these symptoms are severe. For example, Einbinder<sup>27</sup> described a patient whose dizziness caused her to fall into furniture. Dizziness/light-headedness appears to be the most common symptom that occurs on SSRI discontinuation. Although dizziness has been described on discontinuation of tricyclic antidepressants, it is far less prominent, occurs less frequently, and tends to be less severe than when associated with cessation of SSRIs.

Sensory abnormalities comprise the second novel symptom group and include shock-like sensations, paresthesia, and numbness. The shock-like sensations have been described as "a jolt," "a rush," or "a shock,"<sup>28</sup> like "electric shocks" or "electric-like waves"<sup>29</sup> and may occur in up to 5% of patients who stop taking an SSRI.<sup>28</sup> Coupland et al.<sup>17</sup> suggest that they may be a severe form of paraesthesia. Several reports<sup>17,29</sup> mention that the shocks may be exacerbated by slight movement, and, in some cases, they are very disabling.<sup>29</sup> Shock-like sensations are not described in the literature on tricyclic antidepressant discontinuation.

Aggressive and impulsive behavior may represent a third novel symptom cluster seen on SSRI discontinuation. However, the occurrence of this cluster is based on only three case reports of SSRI discontinuation,<sup>30,31</sup> far fewer data than those which support the existence of the two novel symptom clusters described previously. Thus, the association may be coincidental or, if causal, extremely rare. Further verification is required before one can confidently regard impulsive and aggressive behavior as a recognized feature of SSRI discontinuation.

Symptoms of SSRI discontinuation seldom appear in isolation. Rather, a group of symptoms may overlap markedly; some will fall within the Dilsaver et al.<sup>2</sup> classification, and some may be part of the three novel symptom clusters. This overlap may make the discontinuation phenomena difficult to recognize in clinical practice. In particular, psychiatric discontinuation symptoms such as depressed mood, agitation, or irritability may be mistaken for a relapse of depressive symptoms.

### DIFFERENCES AMONG SSRIs

The variation in incidence of discontinuation reactions among the SSRIs may be partly accounted for by their markedly different pharmacokinetic profiles.<sup>32</sup> Several pharmacokinetic factors appear relevant. First, there is the half-life of the parent drug. Fluoxetine (low risk of discontinuation reactions) has the longest half-life of the SSRIs, while paroxetine (high risk of discontinuation reactions) has one of the shortest half-lives. When multiple doses are assessed, the half-life of paroxetine is 21 hours while that of fluoxetine is almost 6 days. Second, the occurrence of active metabolites may influence the variation in incidence of discontinuation reactions among SSRIs.

Paroxetine has no active metabolite, while norfluoxetine, the active metabolite of fluoxetine, has a half-life of 7 days, which effectively extends the already long half-life of fluoxetine. A third pharmacokinetic factor that may be relevant is whether the SSRI has linear or nonlinear kinetics. When a drug shows autoinhibition (as do both fluoxetine and paroxetine), its pharmacokinetics are nonlinear, and the elimination half-life decreases as the plasma concentration falls. In the case of fluoxetine, the nonlinear kinetics is probably immaterial because of the agent's long half-life. However, in the case of a short half-life agent, such as paroxetine, the occurrence of nonlinear kinetics will result in a precipitous drop in plasma paroxetine levels following drug cessation. In summary, pharmacokinetic factors including short half-life, absence of active metabolites, and autoinhibition may contribute to the high rate of discontinuation symptoms that are seen with paroxetine. These factors may also contribute to the severity of discontinuation phenomena.

Pharmacodynamic differences may also contribute to the differential incidence of discontinuation reactions seen with the SSRIs. Of particular note is the fact that of the five SSRIs, paroxetine has the most affinity for muscarinic-receptor blockade and is also the most potent inhibitor of serotonin reuptake.<sup>33</sup>

### DISCONTINUATION REACTIONS WITH VENLAFAXINE

Venlafaxine is a comparatively new antidepressant that inhibits the reuptake of both noradrenaline and serotonin. Farah and Lauer<sup>34</sup> report that, in phase 2 clinical trials, discontinuation of higher dose venlafaxine resulted in insomnia, headaches, and fatigue in some patients. A number of case reports have also been published describing venlafaxine discontinuation reactions.<sup>34-36</sup> Some of the symptoms described in these case reports are similar to those reported with SSRI discontinuation and include dizziness, headache, nausea, fatigue, excessive dreaming, and, in one case,<sup>35</sup> shock-like sensations which were exacerbated by movement, i.e., one of the novel SSRI symptoms.

One of the three patients reported by Louie et al.<sup>35</sup> was a 46-year-old woman with major depression and no history of hallucinations or psychosis who experienced auditory hallucinations on terminating venlafaxine, which remitted on restarting this medication. Auditory hallucinations occurring as an antidepressant discontinuation symptom are very unusual. Two of the three patients reported by Louie et al. had previously experienced discontinuation symptoms on stopping SSRIs and reported that they regarded those symptoms as similar to those experienced on stopping venlafaxine.

The discontinuation reactions seen with the SSRIs and venlafaxine may share a similar mechanism, as both inhibit the reuptake of serotonin. However, venlafaxine also

inhibits the reuptake of norepinephrine, and this may also be relevant. Venlafaxine has a short half-life and, as with paroxetine, this may contribute to the occurrence of discontinuation reactions.

## CONCLUSIONS

In summary, the data on SSRI discontinuation reactions are derived from published case reports, from data bases of adverse drug reactions that have been spontaneously reported to national monitoring bureaus, and from clinical studies. The incidence of reactions varies widely among the different SSRIs, and there is a general consensus that rates are highest with paroxetine, lowest with fluoxetine, and intermediate for the other SSRIs. The commonest symptoms appear to be dizziness, nausea, lethargy, and headache, but many other symptoms may occur. Some symptoms, such as nausea, lethargy, headache, and insomnia, overlap with the symptoms of tricyclic discontinuation described by Dilsaver et al.<sup>2</sup> However, SSRI discontinuation is also associated with novel symptom clusters, including problems with balance, sensory abnormalities, and possibly aggressive and impulsive behavior. There is a need for more methodologically rigorous studies to characterize the SSRI discontinuation syndrome, determine its incidence and its impact on patients, and evaluate what differences exist among the different SSRIs in terms of these parameters.

*Drug names:* amitriptyline (Elavil and others), clomipramine (Anafanil), fluoxetine (Prozac), fluvoxamine (Luvox), imipramine (Tofranil and others), paroxetine (Paxil), sertraline (Zoloft), trazodone (Desyrel and others), venlafaxine (Effexor).

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## Discussion

**Dr. Kaplan:** I was surprised to hear that discontinuation reactions are not as common for the serotonin selective reuptake inhibitors (SSRIs) as for the tricyclic antidepressants (TCAs). Many physicians have the clinical impression that patients seem to complain more about SSRI discontinuation.

**Dr. Rosenbaum:** Patients are more likely to abruptly stop SSRI treatment because SSRIs are often taken as a single daily dose and because titration, both upward and downward, is standard practice for the TCAs but not for the SSRIs.

**Dr. Lejoyeux:** When people stop taking TCAs, it is often difficult for them to globalize the discontinuation symptoms because some side effects such as dry mouth disappear while other symptoms such as irritability might begin. Patients who are taking SSRIs, on the other hand, seldom experience long-term somatic or psychological side effects and thus are more likely to notice the symptoms of discontinuation.

**Dr. Rosenbaum:** My colleagues and I see the flu-like symptoms frequently during SSRI discontinuation but seldom hear about the intensifying of an affective disorder, which I think is common but seldom reported because patients are likely to attribute it to the absence of treatment rather than to discontinuation. I once saw the adult daughter

of a physician who was taking between 150 and 200 mg/day of sertraline for obsessive-compulsive disorder and mild depression. When she ran out of medicine, she waited for her father to provide her with samples instead of renewing the prescription. Thus, she would recurrently interrupt treatment suddenly for a few days. In addition to dizziness and flu-like symptoms, marked affective distress in the form of uncharacteristic crying spells and paralyzing sadness would develop. These symptoms responded immediately to the reintroduction of sertraline. This pattern was replicated three times despite cautions to avoid sudden discontinuation of the medication.

**Dr. Haddad:** The problems of discontinuation are not unique to the SSRIs, and the incidence, especially for fluoxetine, may be slightly lower than that for either the TCAs or the monoamine oxidase inhibitors. There is, however, a marked differential in the number of discontinuation reactions reported for the various SSRIs: far more are reported for paroxetine than for fluoxetine, and the numbers for fluvoxamine and sertraline fall in between. If a physician were to select the SSRI that is most likely to cause discontinuation symptoms—paroxetine—the discontinuation problem would be similar to and probably no worse than it is for the TCAs. If fluoxetine is chosen as the antidepressant, a discontinuation syndrome is unlikely.