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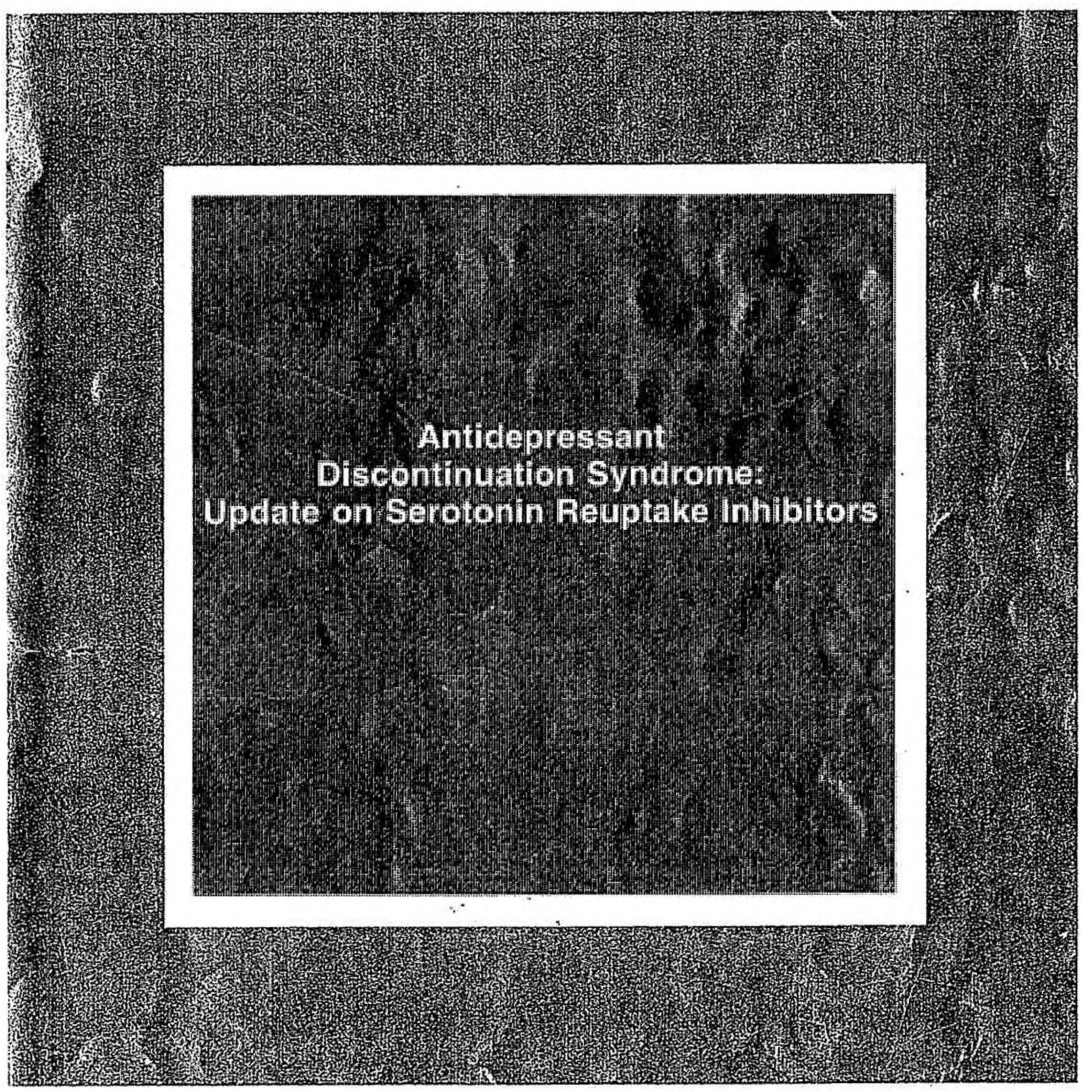
SUPPLEMENT



Celebrating Over 50 Years of Service to Psychiatrists

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Antidepressant Discontinuation Syndrome: Update on Serotonin Reuptake Inhibitors

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Introduction

Antidepressant Discontinuation Syndrome: An Update on Serotonin Reuptake Inhibitors

Alan F. Schatzberg, M.D.

When selecting an antidepressant to treat a patient suffering from depression, a physician should consider the possibility of a discontinuation reaction. Discontinuation symptoms can occur when doses are frequently missed (intermittent noncompliance), upon abrupt cessation of treatment and, less often, during dosage reduction.

These symptoms have been reported with increasing frequency in the literature when the newer serotonin reuptake inhibitors (SRIs) are discontinued. The class of SRIs includes the serotonin selective reuptake inhibitors fluoxetine, fluvoxamine, paroxetine, sertraline, and citalopram (which is marketed in Europe but not the United States); the serotonin-norepinephrine reuptake inhibitor venlafaxine; and the tricyclic clomipramine.

A discontinuation reaction usually involves a cluster of adverse events that generally emerge within 24 to 72 hours after SRI discontinuation and that last, on average, 7 to 14 days. The phenomena, which can be distressing, include both somatic and psychological symptoms. Among the common somatic symptoms are disequilibrium (e.g., dizziness, vertigo), nausea and vomiting, and flu-like symptoms (e.g., fatigue, lethargy). The most frequently reported psychological symptoms are anxiety and/or agitation, crying spells, and irritability.

Symptoms occur more often when patients miss doses or abruptly stop taking an antidepressant than when they slowly taper the agent. Discontinuation reactions are more likely to occur or to become apparent during discontinuation of SRIs that have shorter half-lives than the extended half-life agent fluoxetine. Because discontinuation symptoms are being reported with increasing frequency in the literature, a panel of experts met recently to discuss whether an operationalized definition for a discontinuation syndrome was warranted.

The panel created a hypothetical definition of a proposed discontinuation syndrome. Hallmark features of this syndrome are:

- It is not attributable to other causes.
- It is emergent upon abrupt discontinuation, frequent noncompliance (missed doses), and, less often, after dose reduction.
- It is generally mild and short-lived but can be distressing.
- It can be reversed by the reintroduction of the original medication or one that is pharmacologically similar.
- It is minimized by a slow taper or by using a drug that has an extended half-life.

From the Department of Psychiatry, Stanford University School of Medicine, Stanford, Calif.
Presented, in part, 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.

Michel Lejoyeux, M.D., Ph.D., in a review of the literature, noted that discontinuation reactions occur with most antidepressants and suggested that physicians directly question patients about symptoms that emerge when antidepressant therapy has ended.

Peter Haddad, M.D., noted that the data on antidepressant discontinuation are drawn mainly from anecdotal case reports, spontaneous reports of adverse drug reactions monitored by national surveillance organizations, and a few clinical trials. He also noted that the vast majority of the reports of discontinuation symptoms with the serotonin selective reuptake inhibitors involve paroxetine and the fewest are for fluoxetine.

The panel suggested several potential mechanisms of action. Possible mechanisms for SRI discontinuation reactions include a decrease in available synaptic serotonin in the face of down-regulated serotonin receptors, secondary effects on other neurotransmitters, and biological or cognitive sensitivity in individual patients. In addition, for paroxetine, the symptoms of discontinuation may in part be mediated by a cholinergic rebound effect.

A. H. Young, M.D., Ph.D., in a survey of physicians in the United Kingdom, has found that many general practitioners are unaware that patients may have experienced withdrawal reactions.

Eric Kaplan, M.D., pointed out that noncompliance with therapy is common and thus often leads to discontinuation symptoms. He suggested that physicians could decrease the likelihood of intermittent noncompliance, characterized by missed doses, by spending more time educating patients about their therapy.

Jerrold R. Rosenbaum, M.D., and John Zajecka, M.D., suggested strategies for the clinical management of SRI discontinuation. If the discontinuation syndrome is acute, the original antidepressant dose should be reintroduced and the rate of taper slowed. Gradual taper and the use of an antidepressant with an extended half-life are other methods for minimizing discontinuation symptoms.

While discontinuation symptoms are generally mild and transient, the syndrome can be troublesome, leading to missed work and reduced productivity. It can also be mistaken for new physical illness or the return of the original depression. Misdiagnosing symptoms may lead to costly, unnecessary testing and treatment. Thus, depression treatment guidelines should include information about drug discontinuation, and health care professionals should be educated about the management of symptoms that often accompany SRI discontinuation.

Serotonin Reuptake Inhibitor Discontinuation Syndrome: A Hypothetical Definition

Discontinuation Consensus Panel

Alan F. Schatzberg, M.D., Chair, Peter Haddad, M.D., Eric M. Kaplan, M.D., Michel Lejoyeux, M.D., Ph.D., Jerrold F. Rosenbaum, M.D., A. H. Young, M.D., Ph.D., and John Zajecka, M.D.

Adverse events following discontinuation from serotonin reuptake inhibitors (SRIs) are being reported in the literature with increasing frequency; the frequency and severity of these symptoms appear to vary according to the half-life of the SRI, e.g., the incidence appears higher with the shorter half-life agents than with fluoxetine, which has an extended half-life. Yet, there have been no systematic studies of the phenomenon to date. Therefore, a group of experts convened in Phoenix, Arizona, to develop a clear description or definition of the phenomenon based on these reports. The SRI discontinuation syndrome, referred to as "withdrawal symptoms" in many anecdotal case reports, is distinctly different from the classic withdrawal syndrome associated with alcohol and barbiturates. Antidepressants are not associated with dependence or drug-seeking behavior. SRI discontinuation symptoms tend to be short-lived and self-limiting, but can be troublesome. They may emerge when an SRI is abruptly discontinued, when doses are missed, and less frequently, during dosage reduction. In addition, the symptoms are not attributable to any other cause and can be reversed when the original agent is reinstituted, or one that is pharmacologically similar is substituted. SRI discontinuation symptoms, in most cases, may be minimized by slowly tapering antidepressant therapy, but there have been several case reports where symptoms occurred consistently even through repeated attempts to taper therapy. Physical symptoms include problems with balance, gastrointestinal and flu-like symptoms, and sensory and sleep disturbances. Psychological symptoms include anxiety and/or agitation, crying spells, and irritability. Further analyses of data bases and clinical studies are needed to define this proposed syndrome more clearly. *(J Clin Psychiatry 1997;58[suppl 7]:5–10)*

When patients stop long-term therapy with antidepressants, mood stabilizers, or antipsychotics, discontinuation symptoms frequently occur. These symptoms range in severity from mild somatic distress and gastrointestinal symptoms, which sometimes appear upon tricyclic antidepressant (TCA) withdrawal, to serious cognitive impairment and catatonia that may lead to hospitalization, which can appear when monoamine oxidase inhibitors (MAOIs) are discontinued. However, even when severe, these symptoms are distinctly different from the classic withdrawal syndrome that is associated with sedative hypnotics such as alcohol and barbiturates. Many of the symptoms or symptom clusters that have been reported after discontinuation of the serotonin reuptake inhibitors (SRIs) are similar to those for tricyclic withdrawal, but a variety of novel symptoms are also associated with the stoppage of SRI therapy. Attempts to systematically study SRI discontinuation have been hampered by a lack of an operationalized definition. Thus, the purpose of this article is to create a hypothetical definition of an SRI discontinuation syndrome to facilitate research into a phenomenon that differs dramatically among the SRIs.

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Presented at a 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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WITHDRAWAL VS. DISCONTINUATION

Symptoms of antidepressant withdrawal have long been documented in the literature. Dilsaver et al.[1] reported

Table 1. Hallmark Features of Serotonin Reuptake Inhibitor Discontinuation Syndrome

Not attributable to other causes
Emergent upon abrupt discontinuation, intermittent noncompliance (e.g., missed doses, drug holidays), and, less frequently, with dose reduction
Generally mild and short-lived
Self-limiting but can be distressing
Rapidly reversed by the reintroduction of the original medication or the substitution of one that is pharmacologically similar
Minimized by slow tapering or by using a drug with an extended half-life

five symptom clusters that are associated with TCA discontinuation: general somatic distress, sleep disturbances, akathisia or parkinsonism, behavioral activation, and cardiac arrhythmias. These symptoms were all recorded in a group of seven patients; each subject was systematically evaluated for discontinuation phenomena by the same physician after TCA therapy was stopped abruptly.[2] Severe symptoms such as delirium have been described for MAOI discontinuation.[3] When treatment with serotonin selective reuptake inhibitors (SSRIs) is interrupted, symptoms are most likely to occur for paroxetine[4,5] and least likely for fluoxetine.[6,7] Withdrawal symptoms have also been reported for other antidepressants such as trazodone[8,9] and venlafaxine.[10,11] These symptoms are substantially different from rebound phenomena (such as insomnia or anxiety that return when medication is stopped), depressive relapse, or those associated with withdrawal from sedative hypnotics.

The features of withdrawal associated with sedative hypnotics such as alcohol and barbiturates range from sympathetic overdrive—diaphoresis, tachycardia, jitteriness—to convulsions, coma, cardiovascular collapse, and death. In addition, patients develop tolerance to these medications and display drug-seeking behavior. For example, obtaining alcohol becomes the overriding quest in an alcoholic's life—it eventually takes precedence over going to work and supporting a family. An alcoholic will continue to drink despite overt physical, psychological, and social harm. Physiology probably plays a role in the differences in these symptoms. Barbiturates—but not most antidepressants—have effects on the GABA (gamma-aminobutyric acid) neurotransmitter.

Unfortunately, the public often perceives wrongly that antidepressants—like alcohol and barbiturates—are addicting. In a recent survey of 2000 individuals, Priest et al.[12] found that 78% of those surveyed (N = 2003) thought that antidepressants are addictive and only 1 in 6 believed that depressed people should be offered antidepressant treatment. On the other hand, physicians, particularly those in general practice, are becoming more likely to prescribe antidepressants. Since 1993, the number of prescriptions written in Great Britain for the treatment of depression has increased by 33%, and the number written for SSRIs has risen by 134%,[13] but while more physicians are prescribing antidepressant treatment, few family care physicians and not all psychiatrists are aware that patients who discontinue treatment may experience new symptoms.[14]

HALLMARK FEATURES

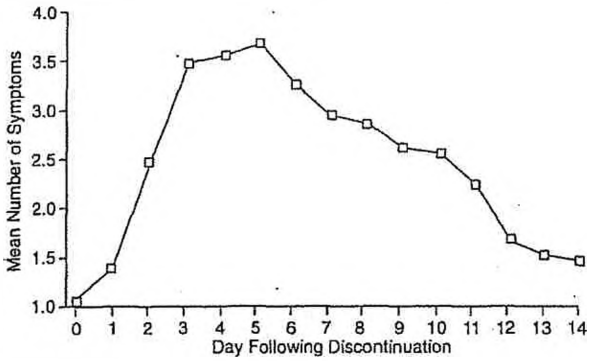
The incidence of discontinuation reactions after SRI cessation varies substantially in published reports. According to a postmarketing survey,[15] the incidence is extremely low (ranging from 0.06% to 5.1% of patients). On the other hand, anecdotal case reports of SRI discontinuation published in the literature have found rates of withdrawal symptomatology as high as 28% of fluvoxamine-treated patients[16] and 50% in a very small series of paroxetine-treated patients.[17] It appears that symptoms have been observed less frequently during abrupt discontinuation of fluoxetine.[6,18–20]

While defining a benzodiazepine withdrawal syndrome, Lader[21] suggested that the syndrome should have a well-defined and predictable onset, duration, and offset. The main characteristics of the proposed SRI discontinuation syndrome are that (1) it is not attributable to other causes; (2) it emerges after abrupt discontinuation, during periods of intermittent noncompliance (missed or forgotten doses), or less frequently, during dose reduction; (3) it is generally mild and transient, but can be troublesome and lead to missed work days and decreased productivity; (4) it is self-limiting; (5) it is rapidly reversed by the reintroduction of the original medication or the substitution of an agent that is pharmacologically similar; and (6) it may be minimized by slow tapering or the use of a drug with an extended half-life such as fluoxetine. (Table 1).

Emergence of New Symptoms

Symptoms of the SRI discontinuation syndrome should not be attributable to other causes. When new adverse events occurred in 5 of 13 subjects who were being tapered from paroxetine after a clinical trial for OCD, Keuthen et al.[22] noted that the symptoms "differed from side effects accompanying the medication trial." The authors further stated that the onset of the new symptoms paralleled the resolution of preexisting medication side effects. In another report,[23] the onset of new adverse effects came 3 days after a patient stopped taking paroxetine. The major side effect of the paroxetine treatment was hypomania, which resolved upon drug discontinuation; however, 3 days later, the patient began to experience anorexia, nausea, diarrhea, and shaking chills. Black et al.[24] noted that 14 subjects, who were assessed for symptoms of fluvoxamine discontinuation, were relatively asymptomatic at baseline when the drug was stopped and that symptoms occurring over the next 2 weeks differed from those at baseline.

Figure 1. Mean Number of Discontinuation Symptoms With Fluvoxamine*



*From reference 24 with permission.

Occurrence of Symptoms

In the vast majority of cases, SRI discontinuation symptoms commence within 1 to 3 days of termination, which is consistent with the half-lives of most SRIs, although symptoms have been reported during systematic tapering and following dosage reduction. Barr et al.[17] studied the effects of a 7- to 14-day paroxetine taper in six patients. Three developed a withdrawal syndrome despite the slow taper. The authors noted that symptoms of withdrawal may occur despite progressive dose reduction of paroxetine. Rauch et al.[11] reported that four of nine patients who were being treated with venlafaxine for obsessive-compulsive disorder (OCD) experienced troublesome symptoms when the dose was incrementally reduced over a period of time ranging from 4 days to 2 weeks. Three consecutive patients who experienced severe physical symptoms of withdrawal during venlafaxine discontinuation were reported by Gaikas and Davis.[25] Repeated attempts at gradually tapering the dosage were unsuccessful and led to intolerable withdrawal sensations. Symptoms occur less frequently and are usually milder in patients who take extended half-life agents such as fluoxetine, but when they occur, onset may be more than 1 week after the final dose. For example, one patient experienced mild dizziness and light-headedness 5 days after she stopped fluoxetine treatment for the first time and 9 days after a second discontinuation.[18]

Severity of Symptoms

While the SRI discontinuation syndrome is usually transient and mild, symptoms, at times, can become serious. Pacheco et al.[26] reported that two of five patients in whom symptomatology developed during paroxetine tapering needed acute treatment. Two other paroxetine-treated patients became manic for 9 to 17 days after treatment was stopped abruptly in one and tapered in the other.[27] After sertraline discontinuation, one patient felt electric shocks of such severity that he momentarily lost control of the steering wheel of his car.[28] Discontinuation symptoms sometimes lead to missed work. After fluvoxamine was abruptly discontinued, 5 of 14 patients who experienced symptoms (including dizziness/incoordination, headaches, irritability, and nausea) were absent from work for at least 1 day.[24]

Persistence of Symptoms

Symptoms of SRI discontinuation are usually short lived; most disappear within 2 weeks, but occasionally the symptoms last for several weeks. In the Black et al. study,[24] patients were evaluated for discontinuation events 5, 10 and 14 days after sudden fluvoxamine discontinuation. Symptoms were most frequently reported on Day 5 and few persisted on Day 14 (Figure 1). The authors of a retrospective chart review of 171 patients who were discontinued from an SRI found that symptoms persisted for a mean of 11.8 days after onset and a maximum of 21 days.[6]

Reversal of Symptoms

If the original antidepressant is reintroduced, or one that is pharmacologically similar is substituted for the original agent, the symptoms of discontinuation remit—usually within 24 hours. Symptoms resolved 1 day after fluoxetine treatment was reinstituted in an elderly woman who had become agitated and disoriented when the medication was temporarily discontinued because of hospitalization,[29] 1 to 2 days after 10 mg/day of paroxetine was restarted in 2 patients,[30] and within 24 hours in those patients who were restarted on their antidepressant in the retrospective chart review.[6] The discontinuation symptoms also remitted abruptly when fluoxetine was started in a patient who had been experiencing severe dizziness after paroxetine cessation.[22] In another patient, fluoxetine was used successfully to treat venlafaxine withdrawal symptoms.[25]

Minimizing the Syndrome

The discontinuation syndrome can be minimized by tapering the shorter acting SRIs extremely slowly or by selecting an antidepressant with an extended half-life such as fluoxetine. Slow taper may be particularly important for paroxetine, fluvoxamine, and venlafaxine, which have half-lives of 24 hours or less. The authors[26] of one report of paroxetine discontinuation symptoms in five young women in whom paroxetine was being tapered over a month noted that withdrawal symptomatology occurred despite conservative tapering and suggested that the paroxetine should be reduced by 5 mg/week—to below the minimum effective dose—to avoid a discontinuation syndrome. To reduce the risk of withdrawal symptoms, tapering of the shorter half-life SRIs fluvoxamine, paroxetine, and venlafaxine thus may have to continue for up to several weeks. Dominguez et al.[31] suggest that the extended half-life of fluoxetine and its active metabolite

Table 2. Core Somatic Symptoms

Disequilibrium, e.g., dizziness, vertigo, ataxia
Gastrointestinal symptoms, e.g., nausea, vomiting
Flu-like symptoms, e.g., fatigue, lethargy, myalgia, chills
Sensory disturbances, e.g., paresthesia, sensations of electric shock
Sleep disturbances, e.g., insomnia, vivid dreams

norfluoxetine protects patients against the emergence of discontinuation symptoms. This would be analogous to the relative lack of serious withdrawal reactions with the benzodiazepines such as chlordiazepoxide that have a long combined elimination half-life as compared with the shorter acting benzodiazepines such as lorazepam and alprazolam that do not have active metabolites.

CHARACTERISTIC SYMPTOMS

SRI discontinuation is characterized by a cluster of somatic and psychological symptoms. Some are similar to the phenomena that have been described by Dilsaver et al.[1] during TCA withdrawal, and some are unique to the SRIs. The manifestation of these symptoms in individual patients often depends on the rate of taper and the half-life of the agent being stopped. None or only a few symptoms might appear in patients who gradually taper the SRI or who are taking a medication with an extended half-life, while a cluster of symptoms is frequent in patients who suddenly stop taking a short half-life SRI.

Most of the symptoms associated with SRI withdrawal are physical rather than psychological. Five clusters of somatic symptoms have been reported frequently in the literature (Table 2): (1) disequilibrium (e.g., dizziness, vertigo, ataxia), (2) gastrointestinal symptoms (e.g., nausea, vomiting), (3) flu-like symptoms (e.g., fatigue, lethargy, myalgia, chills), (4) sensory disturbances (e.g., paresthesia, sensations of electric shock), and (5) sleep disturbances (e.g., insomnia, vivid dreams).

The incidence of these symptom clusters have been confirmed by two analyses of existing data bases on discontinuation reactions. Coupland et al.[6] conducted a retrospective chart review of 352 outpatients who were treated with one of the SRIs. In the 171 patients who were supervised during drug discontinuation, the most common somatic symptoms were dizziness, paresthesia, lethargy, and nausea, but vivid dreams, insomnia, headache, and movement-related symptoms were also reported (Table 3). Similarly, in an analysis of the United Kingdom data base of 271 spontaneously reported discontinuation reactions,[15] somatic symptoms were varied and included dizziness, paresthesia, tremor, nausea, and palpitations. Additionally, Lane[32] noted in a review of the literature on discontinuation that dizziness, sweating, nausea, insomnia, tremor, and headache have all been reported after SRI therapy is stopped.

A number of descriptors have been communicated by patients to describe the physical symptoms associated with SRI discontinuation. Dizziness has been reported as having a "swimming," "spaced out," "drunken," or "buzzing" quality and is often exacerbated by slight movements.[6] Sensory disturbances, which include a feeling of "burning," "tingling," or "electric shocks" have been described. These tend to be localized mainly to the upper half of the body and the face, and they are intense and distracting sensations that usually last a few seconds. Lethargy is occasionally a new symptom of sudden onset and at other times, a worsening of a previous symptom. Sleep disturbances included initial or middle insomnia and vivid or abnormal dreams. Instead of being in black and white, the dreams are often in color and contain frightening images of either self-harm or harm to a loved one. Insomnia, in some cases, represented onset of a symptom that had disappeared previously when the patient responded to antidepressant treatment.

As well as the somatic symptoms, several core psychological symptoms—anxiety/agitation, crying spells, and irritability—are associated with SRI discontinuation (Table 4). Anxiety/agitation was listed as frequent in the Coupland et al.,[6] Price et al.,[15] and Lane[32] reports, and Coupland et al. and Lane both described irritability as a common symptom. The crying spells, in particular, are dramatic and disappear quickly when the SRI is reintroduced.[31]

A number of other psychological phenomena are also noted in the literature about SRI discontinuation phenomena, but cannot be considered as core symptoms of SRI discontinuation. They include overactivity, depersonalization, lowered mood, memory problems, confusion, and decreased concentration and/or slowed thinking.

RISK FACTORS

Use of an antidepressant with a short half-life may be an important risk factor for SRI discontinuation events. The majority of reports of discontinuation reactions drawn from national data bases of spontaneously reported events[4,5,15] involve paroxetine, which has a half-life of 21 hours as compared with over 3 days for fluoxetine, the SRI with the longest half-life and the one involved in the fewest reports of discontinuation reactions. However, one cannot rule out the effects of differences in when specific agents were introduced into the market on reporting of incidents. Still, Coupland et al.[6] found that patients discontinuing the shorter half-life SSRIs, paroxetine and fluvoxamine, were significantly more likely to experience dizziness, paresthesia, lethargy, nausea, and movement-related symptoms than those discontinuing sertraline and fluoxetine. Frost and Lal[28] proposed that the extended half-life of fluoxetine may account for why patients are less likely to experience symptoms when fluoxetine treatment is stopped.

Table 3. Frequency (%) of Specific Somatic Symptoms During SRI Withdrawal*

	Clomipramine (N = 13)		Paroxetine (N = 59)		Fluvoxamine (N = 43)		Sertraline (N = 45)		Fluoxetine (N = 20)
Symptom	N	%	N	%	N	%	N	%	%
Dizziness	2	7.7	8	16.0	4	9.3	1	2.2	0.0
Paresthesia	4	30.8	6	12.0	1	2.3	0	0.0	0.0
Lethargy	1	7.7	6	12.0	2	4.7	0	0.0	0.0
Nausea	2	15.4	3	6.0	3	7.0	0	0.0	0.0
Vivid dreams	2	15.4	2	4.0	3	7.0	0	0.0	0.0
Insomnia	2	15.4	2	4.0	1	2.3	0	0.0	0.0
Headache	0	0.0	0	0.0	3	7.0	0	0.0	0.0
Movement-related	0	0.0	8	16.0	3	7.0	0	0.0	0.0

*Adapted from reference 6. Abbreviation SRI = Serotonin reuptake inhibitor.

Table 4. Psychological Symptoms

Core
- Anxiety/agitation
- Crying spells
- Irritability

Also reported
- Overactivity
- Depersonalization
- Decreased concentration/slowed thinking
- Lowered mood
- Confusion
- Memory Problems

Length of antidepressant treatment is another factor that may affect risk. Coupland et al.[6] noted that symptoms occurred significantly more frequently in patients who had been taking antidepressants for 2 months or more than in those whose treatment was of a shorter duration. Fava and Grandi[7] also reported that withdrawal syndromes tend to occur only after 3 to 4 months of paroxetine treatment. Clinical experience indicates that patients who have had discontinuation symptoms once are likely to do so again and that the phenomenon is more likely to occur in patients with a history of noncompliance to antidepressant medication. Finally, patients who show treatment-emergent anxiety symptoms may be more likely to have symptoms upon SRI discontinuation.

CONCLUSION

The frequency of reports of symptoms that occur during SRI discontinuation is increasing. Thus, a definition or description of the "syndrome" has been proposed. The syndrome may emerge when SRIs are discontinued suddenly, when doses are missed or forgotten, or, occasionally, when doses are lowered. It is not attributable to other causes, is generally mild and short-lived, and is self-limiting, but it can be distressing. Withdrawal symptoms are rapidly reversed by the reintroduction of the original medication or one that is pharmacologically similar and can be minimized by slow tapering or by using a drug with an extended half-life. Physical symptoms include problems with balance; nausea and vomiting; fatigue, lethargy, myalgia, and chills that feel like the flu; and sensory and sleep disturbances. Psychological symptoms include anxiety, irritability, and crying spells.

Controlled studies of SRI discontinuation in large numbers of patients are needed and are underway to test this hypothetical definition and to answer several further research questions such as:

- Does the discontinuation syndrome vary in prevalence or in form among the SRIs?
- Do the number of symptoms and the severity differ in patients with specific disorders?
- Does the antidepressant dose correlate with the risk of the discontinuation syndrome?

Drug names: alprazolam (Xanax), chlordiazepoxide (Librium and others), fluoxetine (Prozac), fluvoxamine (Luvox), lorazepam (Ativan and others), paroxetine (Paxil), sertraline (Zoloft), trazodone (Desyrel and others), venlafaxine (Effexor)

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Discussion

Dr. Zajecka: A syndrome is a cluster of symptoms. We've identified a cluster of symptoms that appear on discontinuation and sometimes even after lowering the dose. I think this cluster of symptoms can be defined as a discontinuation syndrome.

Dr. Rosenbaum: Our hypothesis will soon be able to be tested in extant data bases. One of these data bases is already compiled, and an analysis of discontinuation reactions in 50 patients who stopped SSRI treatment is being prepared. In another study now under way, patients are being discontinued from treatment early and late in the course of treatment. This double-blind study is being conducted at several centers.

Dr. Haddad: In your research, have you seen that this syndrome has diverse manifestations?

Dr. Rosenbaum: Yes, and there are still many open questions. Is the syndrome subtly different for different agents? For different subtypes of patients? For different doses and durations of treatment?

Dr. Zajecka: We need to establish a definition of a sensory disturbance. The literature discusses both paresthesias and electrical sensations.

Our purpose is to encourage clinicians to think about the possibility of discontinuation symptoms and to not misdiagnose patients who come in to report fatigue as having a recurrence of depression. Lethargy, headache, myalgias, and chills are all commonly reported symptoms, and clinicians are likely to understand the term "flu-like."

Dr. Rosenbaum: If clinicians remember disequilibrium, gastrointestinal and flu-like symptoms, and sleep and sensory disturbances, they will have a good picture of the discontinuation syndrome, according to our proposed definition.

Dr. Schatzberg: The existing studies are nonprospective and lack a baseline list of symptoms for researchers to use to discover whether a patient who is experiencing excitement on discontinuation is a person who was excited before starting treatment.

Dr. Kaplan: We have not discussed discontinuation symptoms associated with venlafaxine sufficiently, because data on this phenomenon are lacking. However, in clinical practice, we are frequently seeing discontinuation symptoms associated with a reduction in the dose of venlafaxine.

Dr. Zajecka: Most analyses of reported discontinuation phenomena fail to include venlafaxine, although I have seen patients with discontinuation symptoms 12 hours after they miss a venlafaxine dose.

Dr. Rosenbaum: Discontinuation events occur dramatically and commonly when the venlafaxine dose is adjusted downward as well as on discontinuation.

Mauricio Fava, M.D., and I conducted a prospective study of antidepressant discontinuation at the Massachusetts General Hospital. The symptoms that emerged during venlafaxine discontinuation were dizziness, hot and cold flashes, excessive sweating, nausea, unsteady gait, headache, irritability, dysphoria, and insomnia—the same symptoms that keep appearing after SSRI discontinuation.

Dr. Zajecka: The prescribing information for venlafaxine recommends that, to minimize the risk of discontinuation symptoms, the medication be tapered if patients have been taking it for more than 1 week.

Antidepressant Discontinuation: A Review of the Literature

Michel Lejoyeux, M.D., Ph.D., and Jean Adès, M.D.

Sudden or tapered withdrawal from treatment with antidepressants, including monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs), and serotonin selective reuptake inhibitors (SSRIs), can produce phenomena consisting of somatic and psychological symptoms. The literature about these discontinuation phenomena consists mainly of case reports and a limited number of controlled prospective studies. The symptoms are generally mild and transient for the TCAs and the SSRIs but may be serious for the MAOIs. They are much more common with a shorter acting SSRI, such as paroxetine, than with the longer acting agent fluoxetine. Because the symptoms of antidepressant discontinuation include changes in mood, affect, appetite, and sleep, they are sometimes mistaken for signs of a relapse into depression. Thus, it is important to directly question patients about new symptoms that occur during antidepressant discontinuation to optimally manage treatment discontinuation.
(J Clin Psychiatry 1997;58[suppl 7]:11–16)

For more than 25 years, physicians have known that abrupt or tapered withdrawal from antidepressants can produce discontinuation phenomena consisting of somatic and psychological symptoms. Flu-like symptoms; gastrointestinal distress, including nausea and vomiting; arrhythmias; anxiety; sleep disturbances; movement disorders; mania or hypomania; panic attacks; and delirium have all been reported after antidepressant withdrawal. The symptoms produced by the withdrawal of tricyclic antidepressants (TCAs) and serotonin selective reuptake inhibitors (SSRIs) are generally mild and transient but can be troubling, resulting in decreased productivity and missed work.

In addition, discontinuation symptoms may include changes in mood, affect, appetite, and sleep, which may be incorrectly interpreted as symptoms of a relapse into depression. Patients who are classified as having a relapse while they are discontinuing therapy may, in fact, be suffering from unrecognized discontinuation symptoms.

The literature about antidepressant discontinuation phenomena primarily comprises anecdotal case reports and a few controlled studies. These reports illustrate the importance of directly questioning patients about new symptoms that may emerge during discontinuation. This systematic inquiry will allow both psychiatrists and primary care physicians to reliably document withdrawal symptoms and to optimally manage treatment discontinuation.

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DISCONTINUATION SYNDROME

Malcolm Lader in 1983[1] defined a discontinuation syndrome as having a "predictable onset, duration, and offset of action containing psychological and bodily symptoms not previously complained of by the patient." The symptoms are unrelated to relapse or recurrence, and proper diagnosis requires quantitative assessment of symptoms before treatment and during antidepressant discontinuation. When patients present with these symptoms during the discontinuation phase of treatment, the physician must decide whether to temporarily increase the antidepressant dose, reinstitute the treatment, prescribe medication for symptomatic relief, switch to an alternative agent, or merely reassure the patient that the symptoms will be transient. Patients who present with these symptoms should be closely monitored by the physician.

Antidepressant discontinuation events were first reported by Andersen and Kristiansen in 1959.[2] The first cases of antidepressant discontinuation events were reported for imipramine. Over the past 25 years, the phenomena have been reported with MAOIs, other TCAs, and SSRIs, in particular the shorter acting SSRI paroxetine. There are several risk factors for experiencing discontinuation symptoms. Patients taking high doses of antidepressant therapy may be at increased risk, as well as those who have been treated for a long period of time. For a first episode of depression, the U.S. Depression Guideline Panel[3] recommends that patients be maintained on the therapeutic antidepressant dose for 4 to 9 months. In addition, children and adolescents who are taking antidepressants could be at

higher risk than adults for discontinuation events. The prevalence of symptoms reported after antidepressant discontinuation ranges from 0% in a study of mianserin[4] to 100% in an investigation of imipramine interruption in 22 adolescents[5] (Table 1).[2,4–16] In more recent informal reports involving serotonin reuptake inhibitors, the incidence rates vary between 0% for fluoxetine,[6] 50% for paroxetine,[7] and 86% for fluvoxamine.[17]

In 1987, Dilsaver et al.[18] proposed five categories of symptoms that appear after tricyclic interruption: general somatic distress associated with anxiety (e.g., anorexia, nausea, emesis, diarrhea, diaphoresis, headache, chills, asthenia), sleep disturbances (e.g., insomnia, excessive and vivid dreams), movement disorders (e.g., akathisia, parkinsonism), behavioral activation (e.g., mania or hypomania, panic attacks, and delirium), and cardiac arrhythmia. Behavioral activation, which occurs frequently with TCAs, is especially important. These patients present with discontinuation-related manic or hypomanic episodes. Symptoms of discontinuation from MAOIs are particularly severe and include delirium, thought disorganization, depression associated with cognitive impairment, mania, hypomania, aggressiveness and irritability, agitation, insomnia, and myoclonic jerks.[19] Paranoid delusions as well as visual, olfactory, gustatory, and tactile hallucinations are often observed in schizophrenic patients who are stopping MAOI treatment for depression.

SSRI discontinuation events, in contrast, are frequently transient and mild but can be very distressing. They occur more often with the shorter half-life agents (paroxetine, sertraline, and fluvoxamine) than the extended half-life agent fluoxetine.[20] The most common symptoms are anxiety, irritability, and flu-like symptoms (rhinorrhea, myalgia, malaise, nausea, emesis, diarrhea, shaking chills). Patients described the most frequent symptom, dizziness, as having a "swimming," "spaced-out," "drunken," or "buzzing" quality that could be markedly exacerbated by movement. Paresthesia, the next most common symptom, was reported as "burning," "tingling," or "like electric shocks."[6] In addition, some patients noted lethargy as a new symptom of sudden onset. Others described vivid dreams or nightmares or initial or middle insomnia. While the dreaming was generally a new symptom, the insomnia often represented a deterioration in patients whose sleep had recovered during antidepressant treatment.

Discontinuation symptoms occur more frequently in patients who suddenly stop antidepressant treatment as opposed to those whose treatment is gradually tapered by their physicians. Patients may leave their medication at home when they go on vacation or forget to take their pills and experience a discontinuation event a few days later. The incidence is lower in patients who follow a tapering regimen established by their physicians than in those who suddenly stop taking the medication, but there have been several case reports where patients experienced untoward events during slow tapering[7,21] and at low doses of these antidepressants.[22]

Table 1. Incidence of Symptoms After Antidepressant Discontinuation*

Author	Drug	N	Incidence (%)
Andersen and Kristiansen[2]	Imipramine	85	21.5
Kramer et al[11]	Imipramine	45	55.0
Law et al[5]	Imipramine	22	100.0
Tyrer[13]	TCA		29.4
	Phenelzine	51	32.2
Bialos et al[12]	Amitriptyline	17	80.0
Geller et al[14]	Nortriptyline	36	16.0
Diamond et al[15]	Clomipramine	20	33.3
Otani et al[4]	Mianserin	...	0
Ceccherini-Nelli et al[16]	TCA	10	70.0
Mallya et al[10]	Fluvoxamine	17	28.0
Barr et al[7]	Paroxetine	6	50.0
Keuthen et al[8]	Paroxetine	13	38.5
Coupland et al[6]	SSRIs	158	
	Paroxetine, fluvoxamine	93	17.2
	Fluoxetine	20	0
	Sertraline	45	1.5
Oehrberg et al[9]	Paroxetine	55	34.5

*Abbreviations: SSRI = serotonin selective reuptake inhibitor; TCA = tricyclic antidepressant.

SSRI DISCONTINUATION

Paroxetine

The SSRI discontinuation phenomena have been relatively well documented since 1993, when D'Arcy[23] reported a case of dystonia in a patient who stopped treatment with paroxetine. Since that time, other authors have noted flu-like symptoms similar to those described for TCA discontinuation in patients who are discontinuing SSRIs. Barr et al.,[7] in 1994, described flu-like symptoms in three of six patients who were being tapered from paroxetine treatment of obsessive-compulsive disorder (OCD). During the 7- to 10-day taper, the patients presented with vertigo, light-headedness, rhinorrhea, severe nausea, vomiting, diarrhea, fatigue, insomnia, and myalgia. Keuthen et al.[8] reported on 5 of 13 patients who experienced the onset of adverse events following taper, 1 to 3 days after paroxetine discontinuation. In 1 of these patients, the symptoms remitted abruptly in 1 week after 20 mg/day of fluoxetine was added. These symptoms, particularly nausea and vomiting, are similar to those reported after TCA discontinuation. In another report,[24] flu-like symptoms as well as vertigo, gait instability, hypnagogic visual hallucinations, insomnia, and psychomotor agitation developed after drug discontinuation in three of five paroxetine-treated patients.

Discontinuation symptoms also emerged in 34.5% of patients after a 12-week, double-blind, placebo-controlled clinical trial (patients were taking between 20 and 60 mg of paroxetine per day) evaluating its use for panic disor-

der.[9] The most commonly reported adverse event was dizziness. At the end of a 6-week clinical trial for the treatment of stuttering,[25] two patients became manic (symptoms included shoplifting, overconfidence, and pathologic euphoria). The episodes lasted for 9 to 17 days and remitted spontaneously. Other symptoms that have been reported during paroxetine discontinuation include anorexia, nausea, diarrhea, and shaking chills,[26] electric shock sensations,[27] and headache, nausea, and vomiting 3 days after a patient was switched from paroxetine to sertraline.[28] Discontinuation symptoms have also been observed in patients who had been taking a relatively low dose of paroxetine. Debattista and Schatzberg[22] observed flu-like symptoms in two patients 1 to 2 days after 10 mg/day of paroxetine was discontinued.

Fluvoxamine

Several reports of discontinuation symptoms after fluvoxamine treatment have been published. The half-life of a single dose of fluvoxamine—11 hours—is similar to that for the short-acting paroxetine—10 hours.[29] Mallya et al.[10] reported that 4 of 17 patients who had been treated with fluvoxamine for OCD for 12 months presented with dizziness, nausea, headaches, confusion, memory problems, and weakness when the medication was tapered. Symptoms in all but 1 patient remitted within several weeks. Fluvoxamine was restarted in the patient whose symptoms continued, and the symptoms remitted. Twelve of 14 patients who abruptly stopped taking 300 mg/day of fluvoxamine after 8 months of therapy for panic disorder experienced dizziness, incoordination, headache, nausea, and irritability.[17] The symptoms developed within 24 hours of discontinuation. These patients were probably at increased risk for discontinuation symptoms since they had been taking relatively high doses for a long period of time. In 1994, Ayd[30] also noted mild and transient dizziness, sweating, nausea, insomnia, tremor, and confusion in patients who stopped taking fluvoxamine.

Sertraline

Discontinuation symptoms associated with the cessation of sertraline were first reported in 1994.[31] A 47-year-old woman suddenly ceased taking 100 mg/day of sertraline. Two days later, the patient reported fatigue, abdominal cramps, insomnia, increased dreaming, flu-like symptoms, and impairment of short-term memory. The symptoms disappeared after 25 mg/day of sertraline was reintroduced. Frost and Lal[27] described a patient who presented with sensations of "electrical shock" and complaints of "being electrocuted" 2 days after sertraline was discontinued following a tapering period. The symptoms continued for 13 weeks. In another report,[24] severe vertigo, gait instability, malaise, headache, and muscle aches developed in a patient, who had been treated with 50 mg/day of sertraline, 5 days after discontinuation. The symptoms subsided within a week. Finally, Leiter et al.[32] described two patients who presented with mood alteration, changes in cognition, headaches, paresthesia, and gastrointestinal symptoms after cessation of 8 to 9 months of sertraline treatment.

Fluoxetine

Fluoxetine discontinuation events are less frequent than those for the other SSRIs. In one report,[33] extrapyramidal symptoms including a tremor and diaphoresis occurred. These symptoms disappeared after 45 minutes during diphenhydramine treatment. Kasantikul[34] described a 68-year-old woman who became agitated and disoriented and had visual hallucinations 48 hours after discontinuing fluoxetine. The symptoms ended 1 day after fluoxetine was restarted. Finally, 9 days after 40 mg/day of fluoxetine was abruptly stopped, a patient experienced dizziness and light-headedness. The symptoms disappeared within 2 days after fluoxetine was restarted.

Venlafaxine

Venlafaxine has been studied recently, and symptoms comparable to those for paroxetine discontinuation have been reported.[35] A 32-year-old woman abruptly discontinued taking 300 mg/day of venlafaxine after 8 months of treatment. After 36 hours, she began to suffer from headache, nausea, abdominal distention, asthenia, and the sensation that her "sinuses were congested." The symptoms disappeared 2 hours after a 100-mg dose of venlafaxine was administered, and they reappeared twice more when venlafaxine discontinuation was attempted. In another report,[36] four of nine patients who completed a 12-week trial of venlafaxine for OCD experienced troublesome discontinuation symptoms. Despite a period of taper that lasted from 4 days to 2 weeks, the patients experienced a flu-like syndrome with muscle aches, fatigue, headache, nausea, and dizziness. Symptoms were relieved after venlafaxine was resumed and then tapered more gradually. Data from a double-blind discontinuation study of venlafaxine[37] indicate that the rates of discontinuation-related events were significantly higher in patients who discontinued the drug compared with placebo.

The manufacturer recommends that venlafaxine treatment be tapered gradually and that the patient be monitored during drug discontinuation because a cluster of symptoms, including asthenia, dizziness, headache, insomnia, nausea, and nervousness, occurred as new symptoms during discontinuation in 5% of patients studied in a retrospective survey of premarketing studies.[38] Discontinuation symptoms begin earlier in patients who stop taking venlafaxine than in those who stop taking paroxetine or fluvoxamine. Patients who skip doses often report that discontinuation symptoms appear within 24 hours. Although time to onset of symptoms with paroxetine or fluvoxamine discontinua-

tion is generally 2 or 3 days, symptoms sometimes emerge during venlafaxine dose adjustments and are frequent after sudden discontinuation.

Comparative Studies

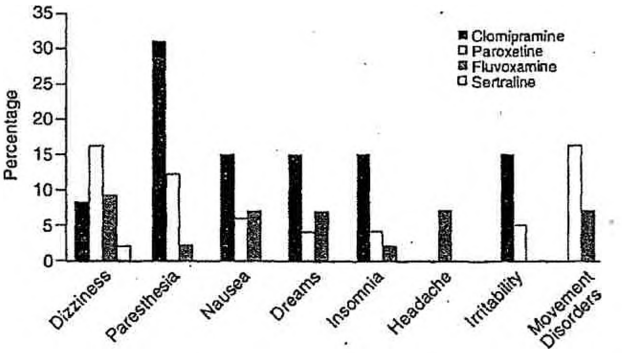
Coupland and collaborators[6] compared discontinuation symptoms by conducting a retrospective chart review of 352 outpatients treated with a serotonin reuptake inhibitor. The patients with at least one qualitatively new symptom were defined as experiencing a discontinuation event. The authors found that symptoms occurred more frequently in patients who had been treated with one of the shorter half-life SSRIs—fluvoxamine or paroxetine—or with clomipramine than in patients taking an SSRI with an extended half-life. In this analysis, 30.8% of the clomipramine treated patients, 14.0% of the fluvoxamine-treated patients, and 20.0% of the paroxetine-treated patients experienced the discontinuation syndrome, as opposed to 2.2% of the sertraline-treated patients and 0.0% of the fluoxetine-treated patients (Figures 1 and 2).

Of the 352 patients, 171 (48.6%) discontinued treatment under supervision, and at least one new symptom (dizziness, paresthesia, or, in one patient, nightmares) emerged in 21 patients despite slowly tapered withdrawal. In this analysis, no adverse events occurred after fluoxetine discontinuation. Dizziness and headaches were most frequently reported after paroxetine discontinuation, while paresthesia, nausea, vivid dreams, insomnia, irritability, and movement disorders occurred most often when clomipramine treatment was stopped. The symptoms persisted for up to 21 days after onset and were relieved within 24 hours by restarting the medication. Coupland et al.[6] also described but did not include in the statistical analysis 5 patients who reported symptoms after an unplanned abrupt discontinuation—generally caused by forgetfulness—of paroxetine. Dizziness was reported by 4, paresthesia by 2, and irritability, nausea, headache, and blurring of vision on movement were each reported by 1 patient.

When they examined the United Kingdom data base of adverse drug reactions for discontinuation symptoms associated with the cessation of fluoxetine, fluvoxamine, paroxetine, and sertraline, Price et al.[39] found that the discontinuation syndrome was reported most frequently for paroxetine and least frequently for fluoxetine. The number of reports of adverse discontinuation events for fluvoxamine and sertraline were about equal.

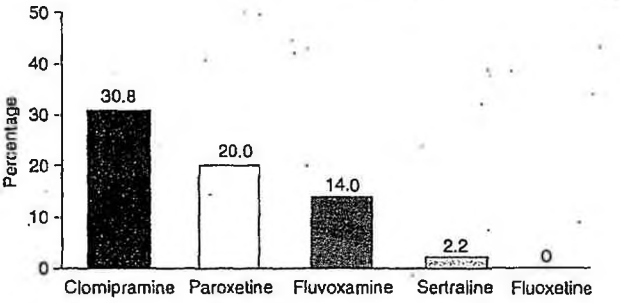
Two other prospective studies of SSRI discontinuation are under way. One multicenter study is in progress; its goal is to mimic the typical intermittent noncompliance that occurs with these drugs to evaluate whether the longer acting drug, in a well-designed prospective study, does have fewer discontinuation events. Another investigation, which was recently completed, examined discontinuation in patients who were in maintenance treatment with sertraline, paroxetine, and fluoxetine. The differences in the incidence and severity of discontinuation events for fluoxetine compared with paroxetine were significantly different.

Figure 1. Incidence of Serotonin Reuptake Inhibitor Discontinuation Symptoms*



*Data from reference 6. There were 13 clomipramine-treated patients, 50 paroxetine-treated patients, 43 fluvoxamine-treated patients, 45 sertraline-treated patients, and 20 fluoxetine-treated patients. No symptoms were reported for fluoxetine, and only dizziness was reported for sertraline. Headache was not reported with clomipramine and paroxetine, irritability was not reported with fluvoxamine, and movement disorders were not reported with clomipramine.

Figure 2. Percentage of Patients Who Experience Serotonin Reuptake Inhibitor Discontinuation Symptoms*



*Data from reference 6. No adverse events were reported for fluoxetine.

CONCLUSION

Any drug that causes adaptive changes in not only the nervous system but in any organ system is likely to be associated with symptoms of discontinuation. However, psychiatrists and other physicians who prescribe psychiatric medications must be especially watchful for the central nervous system effects that sometimes occur during antidepressant discontinuation. MAOIs and TCAs have long been associated with the discontinuation syndrome, and

recent reports have documented symptoms of SSRI discontinuation, particularly when patients are stopping treatment with shorter acting SSRIs such as paroxetine.

Drug names: amitriptyline (Elavil and others), clomipramine (Anafranil), diphenhydramine (Benadryl and others), fluoxetine (Prozac), fluvoxamine (Luvox), imipramine (Tofranil and others), nortriptyline (Pamelor and others), paroxetine (Paxil), phenelzine (Nardil), sertraline (Zoloft), venlafaxine (Effexor)

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Discussion

Dr. Lejoyeux: The literature includes case reports of patients who, for example, forget to take their medication for a weekend. They go on vacation without the pills and experience a discontinuation event a few days later. Although my colleagues and I generally tell patients to taper antidepressants, the patients often choose to simply stop taking the medication when the prescription runs out.

Dr. Schatzberg: Intermittent noncompliance frequently causes discontinuation phenomena. For example, I once gave a patient instructions for tapering venlafaxine. About 10 days later, he called and said, "I haven't been able to get out of bed for about a week because I have terrible vertigo and dizziness." I asked, "How much venlafaxine are you taking?" He responded, "I'm not taking any. I know you told me to taper the medication, but I just stopped taking it."

Dr. Kaplan: In clinical practice, I have seen more incidences of discontinuation symptoms from sertraline than are indicated by the literature. I don't see discontinuation symptoms as often for sertraline as for paroxetine, but I certainly see it more frequently than with fluoxetine.

Dr. Zajecka: At least one case report exists about a woman who took sertraline throughout her pregnancy and was breast feeding [Kent LSW and Laidlaw JDD. Suspected congenital sertraline dependence. Br J Psychiatry 1995;167:412–413]. She stopped breast feeding when the infant was 3 weeks old, and the infant experienced agitation, restlessness, poor feeding, broken sleep patterns, constant crying, and an enhanced startle reaction.

Newer Antidepressants and the Discontinuation Syndrome

Peter Haddad, M.D.

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.

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In 1959, Mann and MacPherson[1] 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.[2–8] 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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INCIDENCE

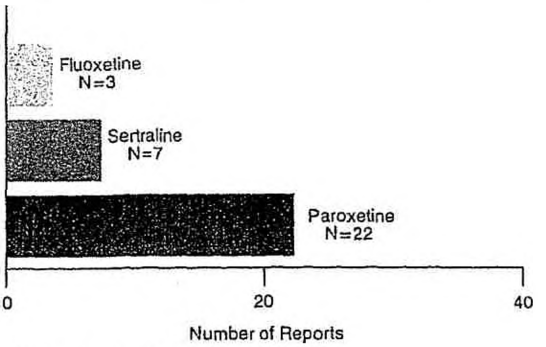
Anecdotal Case Reports

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.[9] described five young women who experienced vertigo, light-headedness, or gait instability during tapered withdrawal from paroxetine.

Adverse Drug Reaction Data

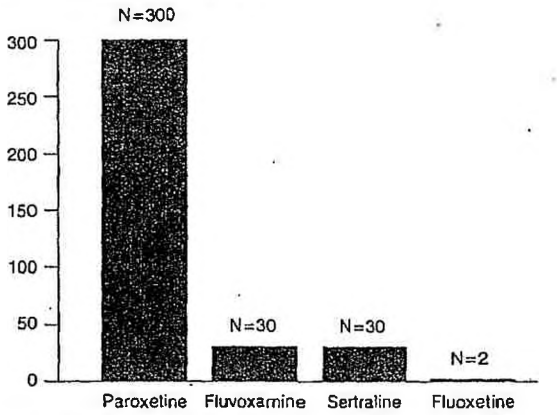
Analysis of data bases of spontaneously reported adverse drug reactions in both the United Kingdom and Australia have also found an excess of reports of discontinuation reactions with paroxetine compared with other

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



*Data from reference 11.

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



*Data from reference 12.

SSRIs. In 1993, the United Kingdom Committee on Safety of Medicines (CSM)[10] 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[11] 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.[12] 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[13] 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 recognized, 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).[14–20] 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.[16] Of particular note are the study by Coupland et al.[17] and that by Oehrberg et al.[20]

Table 1. Studies of SSRI Discontinuation Reactions

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

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

Symptoms of tricyclic discontinuation[a]
- 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.
[a] as classified by Dilsaver et al.[2]

Coupland et al.[17] 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.,[20] 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[21]; 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[22–24] or monoamine oxidase inhibitors,[25] 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 Reactions Advisory Committee,[11] 19 symptoms in the study of fluvoxamine discontinuation by Black et al.,[16] and 10 symptoms in the study by Coupland et al.[17] 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[2] 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.[26]

Several novel symptoms or symptom clusters, which do not fall within the Dilsaver et al.[2] 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.,[17] state that these

symptoms are sometimes exacerbated by slight movement. Occasionally, these symptoms are severe. For example, Einbinder[27] 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,"[28] like "electric shocks" or "electric-like waves"[29] and may occur in up to 5% of patients who stop taking an SSRI.[28] Coupland et al.[17] suggest that they may be a severe form of paraesthesia. Several reports[17,29] mention that the shocks may be exacerbated by slight movement, and, in some cases, they are very disabling.[29] 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,[30,31] 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.[2] 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.[32] 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.[33]

DISCONTINUATION REACTIONS WITH VENLAFAXINE

Venlafaxine is a comparatively new antidepressant that inhibits the reuptake of both noradrenaline and serotonin. Farah and Lauer[34] 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.[34–36] 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,[35] 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.[35] 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.[2] 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 (Anafranil), 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.

Possible Biological Mechanisms of the Serotonin Reuptake Inhibitor Discontinuation Syndrome

Discontinuation Consensus Panel

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Although the number of documented serotonin reuptake inhibitor (SRI) discontinuation reactions is increasing, to date no systematic studies have been completed; therefore the mechanism of action for these reactions is not clearly understood. However, several hypotheses have been proposed. Researchers have postulated that discontinuation events result from a sudden decrease in the availability of synaptic serotonin in the face of down-regulated serotonin receptors. In addition, other neurotransmitters, such as dopamine, norepinephrine, or gamma-aminobutyric acid (GABA), may also be involved, although little research in this area has been published. Individual patient sensitivity, i.e., genetics or cognitive mindset, may also be a factor in SRI discontinuation phenomena. Finally, experts have hypothesized that since some symptoms associated with paroxetine withdrawal are similar to those of tricyclic antidepressant discontinuation, they may be caused by cholinergic rebound.

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Since the efficacy of all available antidepressants is similar, physicians often base their selection of an agent on other factors. One such factor is the likelihood of discontinuation symptoms, which may occur in 30% of patients who discontinue therapy.[1] Both somatic (e.g., problems with balance, nausea and vomiting, sensory and sleep disturbances) and psychological (e.g., anxiety, irritability, crying spells) symptoms have been reported after SRI discontinuation. While available data could suggest that these reactions are more likely to occur with the serotonin reuptake inhibitors (SRIs), such as fluvoxamine, paroxetine, sertraline, and venlafaxine, which have shorter half-lives, than with fluoxetine, which has an extended half-life,[1–3] the exact biological mechanisms of reaction are still unknown. This article will review the existing hypotheses about the mechanisms for these discontinuation symptoms.

MECHANISM OF ACTION FOR SRIs

Serotonin is primarily an inhibitory neurotransmitter utilized by neurons that originate in the raphe nuclei of the brain stem. Each serotonergic neuron sends over 500,000 terminals to the cortex and limbic systems. The diffuse projections of the serotonin pathways allow them to contribute to the regulation of many somatic and psychological functions including appetite, the sleep-wake cycle, sense of pain, mood, anxiety, impulsivity, and aggression. Serotonin also interacts with other neurotransmitter systems, which enhances the capacity of serotonergic systems to influence a broad spectrum of psychobiological functions. For example, the serotonin system has been shown to interact with the gamma-aminobutyric acid (GABA), norepinephrine, and dopamine systems,[4] and a change in the amount of available serotonin may affect these other systems.

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Table 1. Selectivity of Serotonin Reuptake Inhibitors (SRIs) at Blocking Synaptosomal Uptake of Serotonin Over Norepinephrine*

SRI	Selectivity[a]
Sertraline	64
Paroxetine	45
Trazodone	26
Fluoxetine	23
Venlafaxine	5.4
Clomipramine	5.2

*Adapted from reference 5.
[a]Ratio of K_is = K_i uptake norephinephrine/K_i uptake serotonin.

Table 2. Potency of Serotonin Reuptake Inhibitors (SRIs) at Blocking Uptake of Serotonin*

SRI	Potency[a]
Paroxetine	136
Sertraline	29
Clomipramine	18
Fluoxetine	8.3
Venlafaxine	2.6
Trazodone	0.53

*Adapted from reference 5.
[a]10^{-7} x $1/K_i$, where K_i = inhibitor constant in molarity.

Serotonin has been implicated in the mechanisms for affective illness ever since investigators discovered that one of the effects of the tricyclic antidepressants (TCAs) was the blockade of the uptake of serotonin at the presynaptic nerve ending. This discovery became a cornerstone of biogenic amine hypotheses of affective illness, which, in simple terms, suggest that a deficiency or dysregulation of specific biogenic amines at functionally important synapses causes depression. Thus, neuroscientists set out to create a new class of antidepressants that selectively blocked the uptake of serotonin in order to enhance its neurotransmission.

This next generation of antidepressants (serotonin selective reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors) is more potent at blocking the uptake of serotonin than of norepinephrine. In 1994, Richelson[5] created a selectivity ratio that defined six drugs that block the uptake of serotonin more than they do the uptake of norepinephrine (Table 1); the agents include the serotonin selective reuptake inhibitors (SSRIs) fluoxetine, paroxetine, and sertraline as well as clomipramine (marketed in the United States as an antiobsessional and in Europe as an antidepressant), trazodone, and venlafaxine. Fluvoxamine and citalopram are also SSRIs. Fluvoxamine received Food and Drug Administration approval after Richelson created the list, and citalopram is marketed in Europe. This selectivity ratio is derived from data that establish the potency of antidepressants at blocking uptake of norepinephrine and serotonin into rat brain synaptosomes.

The primary action of these drugs is presumed to be blockade of serotonin uptake, although some (e.g., venlafaxine, clomipramine, trazodone) also have known effects on other uptake sites or receptors. The SSRIs—fluoxetine, paroxetine, sertraline, and fluvoxamine—show high affinity for serotonin reuptake sites. Paroxetine is also the most pharmacologically potent antagonist at the serotonin reuptake site (Table 2). Price et al.[2] suggest that this potency may be a significant factor in the frequency of discontinuation reactions for paroxetine as compared with the other SRIs. The SSRIs, however, differ in other effects. For example, paroxetine is unique because its affinity for muscarinic receptors is similar to that of imipramine. In addition, sertraline alone among the SSRIs is potent at dopamine uptake blockade.[5]

Table 3. Possible Mechanisms for the Serotonin Reuptake Inhibitor Discontinuation Syndrome

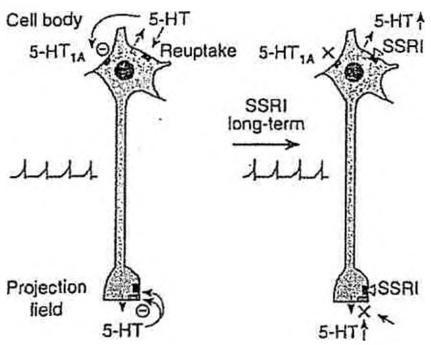
Decrease in available synaptic serotonin in the face of down-regulated serotonin receptors
Secondary effects on other neurotransmitters
Biological or cognitive sensitivity in an individual patient
Cholinergic rebound effect (clomipramine and paroxetine)

During long-term treatment with an SRI, the amount of available serotonin in the frontal cortex increases. Microdialysis studies, which allow for measuring the extracellular levels of transmitter in the frontal cortex and other areas, indicate that low doses of antidepressants with serotonergic action increase the amount of serotonin in the frontal cortex only after repeated treatment.[6] Long-term treatment can also ultimately diminish neurotransmission in the synaptic cleft as the 5-HT postsynaptic receptors undergo compensatory change and become less sensitive to the neurotransmitter (down-regulation).

It has long been recognized that discontinuation symptoms, including gastrointestinal and general somatic distress (sometimes accompanied by anxiety and agitation), sleep disturbances, parkinsonism or akathisia, and paradoxical mania, occur when treatment with tricyclic antidepressants is stopped. Dilsaver[7] suggests that many of these symptoms may be due to cholinergic rebound after cholinergic blockade since tricyclics block cholinergic receptors and induce tolerance. Parkinsonism and akathisia that occur sometimes when TCA therapy is ended may be related to a perturbation of cholinergic/dopaminergic balance. Mania might be a result of cholinergic overdrives that stimulate the limbic activating system.

Symptoms also occur in up to 30% of patients who discontinue treatment with short half-life SRIs. SRI discontinuation reactions may be the result of (1) a decrease in available synaptic serotonin in the face of down-regulated serotonin receptors; (2) secondary effects on other neurotransmitters; or (3) biological or cognitive sensitivity in individual patients. Cholinergic rebound is likely to be a factor in only clomipramine or paroxetine discontinuation since the other SRIs are practically devoid of cholinergic effects (Table 3).

Figure 1. The Serotonin Neuron Before and After Long-Term SSRI Treatment*



*Adapted from reference 8. Abbreviation: SSRI = serotonin selective reuptake inhibitor.

DECREASE IN AVAILABLE SEROTONIN

During long-term SRI treatment, serotonin autoreceptors and postsynaptic receptors are exposed to a high concentration of serotonin because of blockade of the serotonin reuptake pump (Figure 1),[8] which may result in desensitization of the receptors. When SRI therapy is discontinued, serotonin concentrations at the receptors may be decreased, abruptly or slowly, depending on the rate of taper and the half-life of the agent being withdrawn, and there may be a temporary relative deficiency of serotonin in the synapse (lasting from 48 hours to 10 days). Lane[9] proposes that these receptor changes in the serotonin system may correlate with the withdrawal symptoms that have been reported. Coccaro,[10] for example, reported that reduced activity of postsynaptic receptors may correlate with impulsive and aggressive behavior, which have been described during SRI discontinuation.[11]

Many symptoms of SRI discontinuation can be linked to the place of serotonin in biological and psychological function. For example, dizziness and paresthesia may be connected to the purported role of serotonin in coordinating sensory and autonomic functions with gross motor function. Jacobs and Fornal[12] pointed out that the distribution of serotonergic neurons is linked with the structures that are involved in controlling movements that require gross skeletal muscles as well as facial muscles. Paresthesias that have been reported during SRI discontinuation involved the face, neck, or upper body rather than the extremities.[13,14] The serotonergic neurons fire at the same time as or in anticipation of gross movements and are quiescent during REM sleep and orientation. The suppression of some aspects of sensory processing by serotonin could also be a mechanism that underlies the similar suppression during movement, according to Jacobs and Fornal. In support of this theory, many reported withdrawal symptoms intensify upon movement.

Table 4. Half-Life and Active Metabolites of Serotonin Reuptake Inhibitors (SRIs)*

SRI	Half-life (h)	Active Metabolite	Half-Life
Clomipramine	17–28	Desmethylclomipramine	...
Fluoxetine	84	Norfluoxetine	4–16 d
Fluvoxamine	15	None	...
Paroxetine	21	None	...
Sertraline	26	Desmethylsertraline	66 h
Trazodone	4–9	*m*-Chlorophenylpiperazine	...
Venlafaxine	5	O-desmethylvenlafaxine	11 h

*Data from reference 17.

For example, Pyke[15] described a patient in whom eye movement produced visual lag, dyscoordination, and an unpleasant occipital feeling of movement. Dizziness, the most common symptom of SRI withdrawal, is often triggered by slight head or eye movements that could also be related to a disruption of the usual decrease in serotonergic activity during orienting responses.

Coupland et al.[1] suggest that one clue about the nature of the disruption of serotonergic function during SRI withdrawal may be provided by the overlap of dizziness, nausea, lethargy, and visual symptoms with the signs of motion sickness. Motion sickness has been suppressed in animals by 5-HT_{1A} agonists.[16] During chronic treatment with SRIs, desensitization of 5-HT_{1A} receptors in the raphe nuclei occurs,[6] which may lead to greater excitability of serotonergic neurons, mimicking that inferred to occur in motion sickness.

The half-life of the agent being discontinued and the presence of active metabolites may affect the amount of available synaptic serotonin, as suggested by the fact that discontinuation events are more frequent after paroxetine, venlafaxine, and fluvoxamine termination than they are when fluoxetine is discontinued (Table 4).[1,2]

Dominguez[3] noted that the relationship between the frequency of discontinuation reactions and the pharmacologic profiles of the SRIs follows a pattern similar to clinical experience with the benzodiazepines. Withdrawal symptoms are more likely to occur with benzodiazepines that have relatively short half-lives and those without active metabolites (e.g., lorazepam, alprazolam). When Rauch et al.[29] reported on four of nine patients who experienced venlafaxine discontinuation symptoms, they noted that venlafaxine, like paroxetine, has a short half-life. Fluvoxamine also has a short half-life and has been reported to be associated with discontinuation reactions.

The half-life of paroxetine is 21 hours, of fluvoxamine is 15 hours, and of fluoxetine is more than 3 days.[17] The half-life of venlafaxine is 5 hours and of its active metabolite O-desmethylvenlafaxine, 11 hours.[17] Fluoxetine has an active metabolite norfluoxetine, which has a half-life of from 4 to 16 days, while fluvoxamine and paroxetine lack active metabolites.[17] Lazowick[18] proposed that the extended half-life of fluoxetine may prevent the appearance of discontinuation symptoms.

Table 5. Affinities of the Serotonin Reuptake Inhibitors (SRIs) for the Muscarinic Receptor of Human Brain*

SRI	Affinity[a]
Amitriptyline[b]	5.6
Clomipramine	2.7
Imipramine[b]	1.1
Paroxetine	0.93
Sertraline	0.16
Fluoxetine	0.05
Trazodone	0.00031
Venlafaxine	0

*Data from reference 5.
[a] 10^{-7} x $1/k_d$, where K_d = equilibrium dissociation constant in molarity.
[b] Amitriptyline and imipramine, tricyclic antidepressants that have a high affinity for the muscarinic receptor in brain, are shown for comparison.

SECONDARY EFFECTS ON OTHER NEUROTRANSMITTERS

Although little research has been done, there may be secondary effects of discontinuing SRI treatment on other neurotransmitters. For example, Lejoyeux et al.[19] suggested that the extrapyramidal symptoms that have been reported upon fluoxetine discontinuation[20] could be related to serotonin-mediated inhibition of dopamine neurotransmission. Louie et al.[21] theorized that the binding of sertraline to the sigma opioid receptor may be involved in sertraline discontinuation symptoms. Norepinephrine or GABA may also be involved.

INDIVIDUAL DIFFERENCES IN PATIENTS

Individuals may have specific genetic or psychological differences that place them at risk for discontinuation symptoms. When Rosenstock[14] reported on two brothers who experienced similar symptoms when they stopped sertraline treatment, he noted there may be a genetic factor in SRI discontinuation symptoms. For example, 15% of the population lack a serotonin transporter gene; therefore, the perturbing effects of treatment and its discontinuation are likely to be different for these individuals. In addition, cognitive mindset certainly varies among patients. Although several patients may experience similar discontinuation symptoms, some may report these symptoms to a physician while others may tolerate them and not report them.

CHOLINERGIC REBOUND

Several investigators[15,22–24] have suggested that discontinuation symptoms, which have been reported much more often for paroxetine than for the other SSRIs[25] may be the result of cholinergic rebound. Headache, abdominal cramping, and nausea, which occur frequently when tricyclic treatment is ended, have been reported after paroxetine discontinuation.[22,26,27] Unlike the affinity profile for the muscarinic receptor of the other SSRIs, the affinity profile of paroxetine resembles that of the tricyclics (Table 5). However, Fava and Grandi[28] reported on two patients who experienced symptoms after paroxetine discontinuation despite the fact that they had been switched to desipramine, which binds to the muscarinic cholinergic receptor with about the same affinity as paroxetine, which suggests that cholinergic rebound may account for only a part of this phenomenon.

CONCLUSION

SRI discontinuation phenomena are probably due to a decrease in available synaptic serotonin in the face of down-regulated serotonin receptors. However, other neurotransmitters such as dopamine, norepinephrine, or GABA may also be involved. Genetics and cognitive mindset of individual patients are likely to also play a role in the severity of the SRI discontinuation symptoms. Published data suggest that withdrawal symptoms are more likely to occur after paroxetine discontinuation. This increased frequency with paroxetine may in part be due to its being introduced later into the market or to intrinsic pharmacological properties—cholinergic effects, shorter half-life, or pharmacological potency at the serotonin uptake site. Other shorter half-life SRIs (e.g., venlafaxine and fluvoxamine) also appear to be more commonly associated with discontinuation phenomena. Thus, the frequency and severity of symptoms that appear may depend on the pharmacologic profile of a particular drug. Future research is needed to better describe the mechanisms of SSRI withdrawal and to more clearly define the characteristics of this phenomenon.

Drug names: alprazolam (Xanax), amitriptyline (Elavil and others), chlordiazepoxide (Librium and others), clomipramine (Anafranil), desipramine (Norpramin and others), fluoxetine (Prozac), fluvoxamine (Luvox), imipramine (Tofranil and others), lorazepam (Ativan and others), paroxetine (Paxil), sertraline (Zoloft), trazodone (Desyrel and others), venlafaxine (Effexor)

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Physicians' Knowledge of Antidepressant Withdrawal Effects: A Survey

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Background: While the incidence of discontinuation events in controlled studies of serotonin reuptake inhibitors ranges between 34.5% and 86%, only a small number of discontinuation reactions are reported to national data bases of spontaneously reported adverse drug reactions. It was hypothesized that the disparity was due to lack of knowledge amongst physicians about the potential for antidepressant discontinuation reactions. *Method:* Therefore, a questionnaire was mailed to 100 psychiatrists and 100 general practitioners (GPs) in northeast England to assess the knowledge base and to validate this assumption. *Results:* Fifty psychiatrists (50%) and 53 GPs (53%) responded to the questionnaire. Of the respondents, 36 (72%) of the psychiatrists and 16 (30%) of the GPs were aware that patients may experience antidepressant discontinuation events; 33 (66%) psychiatrists and 22 (42%) GPs had had experience with patients who had discontinuation symptoms; and 10 (20%) psychiatrists and 9 (17%) GPs said they always caution patients about the possibility of discontinuation events. *Conclusion:* According to the results of the survey, a sizable minority of physicians denied being confidently aware of the existence of antidepressant withdrawal symptoms. Education about discontinuation reactions, including the hallmark features, symptoms, and course, is needed for both psychiatrists and family practice physicians. *(J Clin Psychiatry 1997;58[suppl 7]:28–30)*

Withdrawal symptoms have been well-described for tricyclic antidepressants, primarily through the work of Dilsaver and colleagues.[1] As the use of the serotonin reuptake inhibitors (SRIs) increased, anecdotal case reports of discontinuation reactions appeared in the literature,[2-4] and several investigators began to study this phenomenon. In 1993, Black et al.[5] evaluated patients who were abruptly terminated from fluvoxamine treatment and found that 12 (86%) of 14 subjects developed new symptoms after discontinuation. At the end of a placebo-controlled clinical trial assessing the efficacy of paroxetine in the treatment of obsessive-compulsive disorder (OCD),[6] 5 (38.5%) of 13 subjects reported the onset of new adverse events during medication taper or within 2 to 14 days after their last dose. Similarly, 19 (34.5%) of 55 patients enrolled in a double-blind, placebo-controlled paroxetine study[7] reported the onset of new adverse events during the 2 weeks after treatment was discontinued.

While reports of SRI discontinuation phenomena have also been published in postmarketing studies based on information from the national data base of spontaneously reported adverse drug events in the United Kingdom[8,9] and Australia,[10] the incidence in these reports appears to be far lower than the 34.5% to 86% of patients reported to experience discontinuation events in controlled studies. This low incidence suggests either underreporting of discontinuation symptoms, lack of recognition of the phenomenon, or both.

We hypothesized that if doctors are not aware of the likelihood that patients will experience symptoms when SRIs are discontinued, they would be unlikely to recognize these symptoms and report them to national surveillance units. This report describes the results of a survey of physicians and psychiatrists undertaken to ascertain the general level of knowledge about antidepressant discontinuation events and, in particular, SRI discontinuation symptoms.

METHOD

We designed a questionnaire (Appendix 1) to elicit information on physicians' awareness of and experience with antidepressant discontinuation events. The 2-page questionnaire was mailed to 100 psychiatrists and 100 general practice physicians in northeast England, who were asked to respond anonymously. Percentages were calculated for each question on the basis of the total number of physicians who answered the question, i.e., blank responses were ignored.

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Table 1. Physicians' Knowledge of and Experience With Antidepressant Discontinuation Events*

	TCA		MAOI		SSRI	
Discontinuation Events	N	%	N	%	N	%
Knew of reports						
Psychiatrists	37	74	39	78	47	94
General practitioners	31	58	25	47	36	68
Have seen patients						
Psychiatrists	21	42	17	34	33	66
General practitioner	20	38	3	6	22	42

*Responses from a survey of 100 psychiatrists (N = 50) and 100 general practitioners (N = 53). Abbreviations: MAOI = monoamine oxidase inhibitor; SSRI = serotonin selective reuptake inhibitor; TCA = tricyclic antidepressant.

Table 2. Physicians' Response to Antidepressant Discontinuation Events*

	Psychiatrist		General Practice Physician	
Response	N	%	N	%
Always or usually advise patients	26	52	27	51
Would report to national surveillance bureau	20	40	26	49
Would write letter to journal	1	3	0	0

*Responses from a survey of 100 psychiatrists (N = 50) and 100 general practitioners (N = 53).

RESULTS

A total of 50 psychiatrists, including 44 consultants in psychiatry and 6 psychiatry trainees, and 53 GPs responded to the questionnaire, although not all the respondents answered every question. Interestingly, 72% of the psychiatrists (N = 36) as opposed to 30% of the GPs (N = 16) said they were confidently aware of the possibility that patients might experience symptoms when they stop antidepressant treatment. In addition, 11% of the GPs (N = 6) and none of the psychiatrists reported that they were unaware of the risk of discontinuation events after antidepressant treatment.

Most physicians (both psychiatrists and general practice physicians) knew of reports about, and a sizable minority had seen, patients with discontinuation symptoms (Table 1). Almost all the psychiatrists (94%; N = 47) knew of reports of discontinuation events associated with serotonin selective reuptake inhibitors (SSRIs), a larger number than knew of reports about monoamine oxidase inhibitor (MAOI) (78%; N = 39) or tricyclic antidepressant (TCA) discontinuation (74%; N = 37). More GPs (68%; N = 36) also knew of reports of SSRI discontinuation events than of MAOI (47%; N = 25) or TCA (58%; N = 31) discontinuation symptoms. In terms of having experience with discontinuation symptoms after antidepressant treatment, 66% of psychiatrists (N = 33) had seen patients with SSRI discontinuation events, 34% (N = 17) had experience with MAOI discontinuation, and 42% (N = 21) had experience with TCA discontinuation. This is opposed to 42% (N = 22) of GPs who had experience with SSRI discontinuation, 6% (N = 3) who had seen patients with MAOI discontinuation symptoms, and 38% (N = 20) who had seen patients with TCA discontinuation events.

While most physicians said they would advise patients about the possibility of discontinuation events, few said they would report these symptoms to a national surveillance bureau or write a letter to a journal (Table 2). Fifty-two percent of the psychiatrists (N = 26) and 51% of the general practice physicians (N = 27) said they always or usually give advice to patients about possible discontinuation symptoms. However, only 1 psychiatrist (3%) and no GPs said they would be likely to write a letter to a journal reporting such symptoms. Fewer than half of both psychiatrists (40%; N = 20) and general practice physicians (49%; N = 26) said they would report discontinuation symptoms to a national adverse drug event monitoring bureau.

DISCUSSION

A sizable minority of psychiatrists and a majority of GPs said they were not confidently aware of adverse events associated with antidepressant discontinuation. This has important implications since physicians who have not heard about these phenomena will not be able to recognize or treat them. While many physicians reported that they generally would advise patients about the possibility of discontinuation events, less than half said that they would record these events with a national surveillance bureau, which may account for the discrepancy between the incidence in postmarketing surveillance data[8–10] and the studies of antidepressant discontinuation[5,6,10,11] Additionally, routinely educating patients about the possibility of antidepressant discontinuation symptoms may be justified since patients often become noncompliant and abruptly stop taking their medication.

One strategy for reducing the likelihood of discontinuation events would be to inform psychiatrists and primary care physicians about the hallmark features, symptoms, and course of these phenomena. In turn, they could take the time necessary to educate their patients on the benefits of good compliance and, equally important, the consequences of intermittent noncompliant behaviors (e.g., missed doses, late refills) that would lead to withdrawal reactions. In addition, physicians must become comfortable with implementing appropriate tapering schedules when discontinuing the shorter acting SRIs such as paroxetine, venlafaxine, and fluvoxamine. Fluoxetine, on the other hand, which has an extended half-life, is much less likely to cause discontinuation-emergent symptoms and, for the most part, tapering is not required for fluoxetine.

Drug names: amitriptyline (Elavil and others), fluoxetine (Prozac), fluvoxamine (Luvox), paroxetine (Paxil), sertraline (Zoloft), venlafaxine (Effexor)

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Appendix 1. Survey of Knowledge of Antidepressant Withdrawal Effects

The purpose of this questionnaire is to survey the knowledge and experience of doctors and pharmacists of withdrawal effects with antidepressants. You are asked to complete the questionnaire by ticking the appropriate boxes **without using any reference source.** Thank you for your cooperation.

What is your area of practice:
Nonconsultant psychiatrist ☐ Consultant/lecturer psychiatry ☐
Hospital pharmacist ☐ General practitioner ☐
Community pharmacist ☐

1) Are you aware of any adverse effects which are likely to occur on cessation of treatment with antidepressants?
Confidently aware ☐ Heard reports, but unsure about likely effects ☐
Not aware of any reports ☐

2) Which, if any, antidepressants have been reported to be associated with withdrawal symptoms?

Tricyclic antidepressants	yes ☐	no ☐
MAOIs	yes ☐	no ☐
SSRIs	yes ☐	no ☐
Other	yes ☐	no ☐

If you have answered yes, please explain by giving some examples. _____

_____

_____

_____

3) Have you had experience of withdrawal effects with antidepressants in any of your patients?

Tricyclic antidepressants	yes ☐	no ☐
MAOIs	yes ☐	no ☐
SSRIs	yes ☐	no ☐
Other	yes ☐	no ☐

If you answered yes, please state which antidepressant and number of occurrences. _____

_____

_____

_____

Please indicate which bodily systems were involved:
CNS ☐ GI ☐ Respiratory ☐ Cardiovascular ☐ Musculoskeletal ☐
Other ☐ (describe briefly) _____

4) What dose of antidepressant would you consider stopping abruptly for the following antidepressants and indicate your usual practice regarding tapering the dose before stoppage? (Complete the table for your usual antidepressants only.)

Antidepressant	Daily does at which you abruptly stop	Taper usually	
Amitriptyline	_____ mg/day	yes ☐	no ☐
Dothiepin	_____ mg/day	yes ☐	no ☐
Lofepramine	_____ mg/day	yes ☐	no ☐
Citalopram	_____ mg/day	yes ☐	no ☐
Fluoxetine	_____ mg/day	yes ☐	no ☐
Fluvoxamine	_____ mg/day	yes ☐	no ☐
Paroxetine	_____ mg/day	yes ☐	no ☐
Sertraline	_____ mg/day	yes ☐	no ☐

5) Do you advise/inform patients and carers of possible withdrawal symptoms on cessation of antidepressant treatment?
Always ☐ Usually ☐ Sometimes ☐ Never ☐

6) If you came across a case of antidepressant withdrawal phenomena would you...

a) Report to the CSM (or government drug surveillance unit)	yes ☐	no ☐
b) Write a letter to a medical journal	yes ☐	no ☐

Antidepressant Noncompliance as a Factor in the Discontinuation Syndrome

Eric M. Kaplan, M.D.

Compliance is generally defined as the extent to which a patient adheres to a treatment regimen and, specifically, takes medication as prescribed. While little research is available about the number of patients who consistently skip antidepressant doses, the literature indicates that about 30% of patients discontinue treatment suddenly within the first month. Both missed doses and abrupt stoppage of treatment place a patient at risk for experiencing discontinuation symptoms. A variety of reasons ranging from forgetfulness to lack of knowledge about the importance of taking every dose may lead to nonadherence to an antidepressant regimen. By spending time on patient education, providing reasons why patients should take every antidepressant dose, discussing alternative treatments, and conveying empathy, support for, and understanding of the patient, physicians may be able to minimize noncompliance and consequently decrease the likelihood that a patient may experience discontinuation symptoms. Discontinuation of an antidepressant can cause a patient to be irritable, experience severe dizziness, or act emotionally absent, which may have a sustained adverse impact both on job performance and on family and social relationships.

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Compliance is generally defined as the extent to which a patient adheres to a treatment regimen and, more specifically, takes medication as prescribed. Noncompliance may consist of a variety of behaviors from consistently skipping antidepressant doses to abruptly stopping medication without informing the physician; these behaviors may lead to discontinuation symptoms.

Patients are at risk for experiencing discontinuation symptoms when they stop taking antidepressants without the guidance of their physicians. A group of investigators in Seattle who examined patterns of antidepressant use found that up to 75% of patients being treated for depression by primary care physicians discontinued medication within 30 days.[1] An analysis of data on the duration of antidepressant therapy for a group of health maintenance organization enrollees, performed by the same research group,[2] showed that 66% of patients failed to fill four or more antidepressant prescriptions within 6 months. Similarly, Priest et al.,[3] reporting on the results of a survey in the United Kingdom on lay people's attitudes toward the treatment of depression, noted that most patients who begin antidepressant therapy abandon it prematurely.

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REASONS FOR BEING NONCOMPLIANT

A patient's compliance with antidepressant medications may be affected by various circumstances including differences among patients, physicians' attitudes, and clinical environments (e.g., acute, continuation, or maintenance treatment; first or second episode of illness vs. treatment-resistant depression). Fawcett[4] listed several reasons for poor medication compliance (which are listed in Table 1) including illness content (e.g., guilt-ridden depressed patients may be reluctant to take medication); physicians who fail to provide adequate reassurance and hope for benefit; a lack of continuity of care, which includes close follow-up during the early stages of treatment; a complicated treatment regimen; the cost of medical care; chronic illness, especially if the depression has remitted and the antidepressant is prophylactic; and comorbid symptoms such as panic attacks, severe anxiety, and alcohol and drug abuse. In addition, some patients occasionally respond to suggestions that appear in the lay press or come from friends to take a "drug holiday" to avoid the sexual side effects of antidepressants.

Efficacy of the agent is a major factor in patient noncompliance, in three different ways. First, some patients are noncompliant because of lack of efficacy of the drug. Individuals who are displeased with their response to antidepressants may stop taking the medication and experience discontinuation symptoms as a consequence. In a study of the relationship of compliance to successful long-

Table 1. Reasons for Patient Noncompliance, According to Physicians' Experience*

- Reluctant to take medication due to guilt
- Physician fails to provide reassurance and hope
- Lack of continuity of care, including follow-up
- Complex treatment regimen
- High cost of medical care
- Chronic illness
- Comorbid symptoms such as panic attacks, severe anxiety, and alcohol and drug abuse
- Displeased with treatment response (efficacy)

*Adapted from reference 4.

Table 2. Reasons Patients Say They Are Noncompliant

- Unaware of the importance of consistently taking the medicine
- Perceive lack of a friendly relationship with the physician
- Too much waiting room time
- Need to take medicine 3 or 4 times daily
- Side effects

term treatment, Frank et al.,[5] who assessed compliance by regularly measuring blood drug levels, found that only 2 of 28 patients who remained well for 3 years were periodically noncompliant as opposed to 6 of 12 patients who experienced a recurrence of depression. Second, some patients discontinue a drug due to a perceived lack of efficacy before it even has a chance to begin working because they think antidepressants work in the same way as analgesics; patients expect to feel better immediately. Third, still other patients are noncompliant even if the agent has been efficacious; patients who have responded well to antidepressants sometimes interrupt treatment abruptly after 3 or 4 months to test whether the medication is still necessary. Since they have usually been warned by their physician that relapse is likely if they do not continue treatment for 4 to 9 months, they often fail to tell their physician about the stoppage.

Patients themselves list a variety of reasons for being noncompliant with treatment (Table 2). Most often they say that they miss doses of medicine because the physician failed to inform them about the importance of taking every dose. They also say their compliance depends on whether they like their physician, how long they spend in the waiting room, how many doses of medicine they are required to take per day, and how uncomfortable the side effects of the drug are. Patients who like their physician are less likely to skip doses than those who do not view their relationship with their doctor as friendly. People who believe they have to wait overly long to see the physician are less compliant than those who are satisfied with their waiting room time. Forgetfulness is particularly common for medication that has to be taken more often than twice a day, but even patients who are taking an antidepressant only once or twice a day sometimes leave home for a few days without their medicine and do not want to bother their physician by calling and asking that a prescription be telephoned to their new location. Finally, patients sometimes say they are noncompliant because of severe side effects of the medication. Side effects usually appear at the beginning of treatment, which may account for the large proportion of patients who discontinue antidepressants abruptly within the first month. In one study,[6] 62% of patients who stopped taking antidepressants during the first month of treatment attributed the discontinuation to severe side effects.

IMPORTANCE OF COMPLIANCE

Guidelines from the U.S. Agency for Health Care Policy and Research[7] recommend that upon remission of depressive symptoms, antidepressant treatment should be continued for 4 to 9 months to minimize the chance of relapse. Maintenance treatment for 1 to several years may also be appropriate for patients who have had three previous episodes of depression or who have had two episodes but also have a first-degree relative with bipolar disorder or recurrent major depression; a history of severe, sudden, or life-threatening depression; or onset before the age of 20 years. If a patient is noncompliant, the likelihood of discontinuation symptoms including sleep problems, agitation, anxiety, and flu-like symptoms, as well as the strong possibility for relapse of their depression, argues strongly against drug holidays or any sudden, temporary discontinuation.

Because of these risks, physicians should be aware of the reasons that patients stop antidepressant treatment and plan several strategies to reduce the likelihood of noncompliance. Patients should be educated about the possibility of experiencing discontinuation symptoms after missing as few as two doses of agents that have shorter half-lives, such as venlafaxine or paroxetine. Physicians themselves need to be more aware of the likelihood of discontinuation symptoms, which are sometimes misdiagnosed as physical illness or mistaken for a recurrence of the primary psychiatric illness. As a result, patients may undergo expensive unnecessary tests or be restarted on treatment for depression. When patients who are being treated with antidepressants report these symptoms, the first question for the physician to ask is, "Have you missed or forgotten to take any doses?"

Recurrence can be differentiated from discontinuation symptoms by the time frame. Discontinuation events tend to occur within 24 or 72 hours of stopping all SRIs (paroxetine, sertraline, fluvoxamine, and venlafaxine) except fluoxetine, while recurrence is unlikely before 2 to 3 weeks after the antidepressant is stopped. Discontinuation symptoms generally remit after 7 to 14 days; they are time-limited and transient. Thus, the likelihood that a patient is experiencing recurrence of illness rather than discontinuation symptoms increases with the length of time from the end of treatment with all SRIs except fluoxetine.

The extended half-life of fluoxetine often provides protection against discontinuation symptoms.

STRATEGIES TO IMPROVE COMPLIANCE

Several clinical strategies can be employed to increase patients' adherence to antidepressant regimens (Table 3). First, physicians should plan time during office visits to teach patients about the nature of depression, how antidepressants work, and the importance of completing the course of treatment. Some of this education can be provided by office staff and by the use of written materials and videotapes. Multiple methods of presentation are extremely important for severely depressed patients whose ability to concentrate is often diminished. Second, patients need to be given reasons why it is important to take every dose of medication, including the possibility of experiencing discontinuation symptoms when several doses are missed or the medication is abruptly stopped. Third, it is important to discuss alternative treatments with patients to reduce the likelihood they will abandon treatment independently because of perceived lack of efficacy. Finally, the physician should effectively communicate empathy, support for, and understanding of the patient since many patients say they are noncompliant because they lack a friendly relationship with their physician. These strategies to prevent noncompliance are described below.

Table 3. Clinical Strategies to Reduce Noncompliance

- Educate patients about the nature of depression, how antidepressants work, and the importance of completing the course of treatment
- Provide reasons why patients should take every dose of the antidepressant (i.e., receive beneficial effects in time, prevent discontinuation symptoms)
- Discuss alternative treatments
- Convey empathy, support for, and understanding of the patient

Table 4. Specific Educational Messages To Improve Compliance*

- It will take 2 to 4 weeks before you notice beneficial effects
- You should continue taking the medication even after you begin to feel better
- Check with your physician before you stop taking the antidepressant
- Take the medication as directed
- Call your physician with questions

*Adapted from reference 6.

Patient Education

Since patients frequently report that they skip doses or temporarily interrupt treatment because they didn't understand that it was important to take every dose of medication, physicians should spend time teaching patients about the nature of depression, how antidepressants work, and the importance of completing the course of treatment. The explanation of the illness should provide a rationale for the use of medication and include an inquiry into the patients' hesitations and fears about taking antidepressants. Patients and family members need to be reassured about potential medication side effects. The expected time until onset of action and the duration of treatment should also be explained. Depressed patients and their significant others should be informed that response to antidepressants may take up to 2 to 4 weeks and that the risk of recurrence is high if treatment is not continued for at least 4 to 9 months. The amount of time spent on patient education is a crucial factor in obtaining compliance to antidepressant treatment.

Studies have shown that medication compliance is increased when health care providers spend additional time with patients, when patients attend educational meetings, and when patients receive written instructions about their regimen.[8,9] For example, 217 depressed patients who enrolled in a 12-month study were randomly assigned to either usual care or intervention groups.[8] The patients in the intervention group met with a physician more frequently than the patients in the usual care group, received booklets on the biology of depression and how antidepressants worked, and saw videotapes that reinforced the information in the pamphlets. These patients were significantly more likely to adhere to a medication regimen for 90 days. In patients with major depression, the intervention group was more likely than the controls to continue taking an antidepressant for 90 days or more (75.5% vs. 50.0%; $p < .01$). Similarly, 79.7% of the patients with minor depression in the intervention group as opposed to 40.4% of the controls adhered to the regimen for 90 days or more ($p < .001$). In an extension of this study,[9] which involved 153 patients, counseling to improve adherence to treatment was provided to those in the intervention group. At 4-month follow-up, intervention patients with major depression were significantly more likely to adhere to antidepressant treatment than the controls (89% vs. 62%; $p < .02$). Intervention patients with minor depression were significantly more likely than controls to report adherence to antidepressant treatment at both 4-month (74% vs. 44%; $p = .01$) and 7-month (65% vs. 41%; $p = .04$) follow-up.

In a study designed to identify specific educational messages that will improve patient adherence to antidepressant therapy, Lin et al.[6] found that patients were more likely to be compliant if they were asked about prior use of antidepressants. Compliance also improved in patients who received the following four specific educational messages (Table 4): (1) It will take 2 to 4 weeks before you notice beneficial effects. (2) You should continue taking the medication even after you begin to feel better. (3) Check with your physician before you stop taking the antidepressant. (4) Take the medication as directed. These patients were more likely to continue treatment if they

Table 5. Strategies To Promote Effective Communication

- Be enthusiastic
- Avoid giving orders
- Individualize your approach by listening to the patient
- Recognize patients who may be at risk for being noncompliant (e.g., guilt-ridden depressed patients, patients who lack social supports)
- Provide information in a variety of formats (e.g., pamphlets, videotapes, workshops, one-on-one)
- Differentiate between the needs of patients who are acutely ill and those who need chronic treatment
- Make sure the information is appropriate for the patient
- Encourage the patient to ask questions
- Find out if the patient understands the instructions, is able to follow them, and intends to follow them.

were instructed to call the physician's when they had questions. The telephone is a useful tool for avoiding unnecessary follow-up visits.

Some patient education can be completed by nonphysicians. The ongoing Pittsburgh Study of Maintenance Therapies,[10] in which about 85% of patients meet stringent compliance criteria for 3 years, uses a treatment team consisting of a nonphysician primary clinician (a psychologist, social worker, or nurse-clinician) and a physician consultant. During the acute and continuation phases of treatment, patients are seen by both the physician and the nonphysician at each visit. During the maintenance phase, the physician generally sees the patient only once every 6 months. In addition, after the acute phase of treatment is over and improvement has been noted, the patient and family members are invited to special psychoeducational workshops.

Provide Reasons for Taking Every Dose

When patients are provided with a series of reasons why it is important to adhere faithfully to a treatment regimen, they will be less likely to forget doses or suddenly stop taking the antidepressant. These reasons include: (1) the beneficial effects of antidepressants that will come within a few weeks; (2) the fact that a reemergence of symptoms, which may appear when treatment is prematurely interrupted, increases the likelihood that treatment-resistance will develop over time; and (3) that discontinuation symptoms may occur, particularly if treatment is interrupted suddenly or several doses are missed. Thus, the more information patients have about potential discontinuation events, the more compliant they will be. The symptoms of discontinuation should be described, and patients should particularly be warned about skipping doses of paroxetine and venlafaxine, which have shorter half-lives. Because the general public generally thinks about medication in terms of an analgesic, which acts almost immediately, patients must be routinely told about the delay in onset of action for antidepressants, in order to reduce the chances that they abandon treatment prematurely and experience discontinuation phenomena.

Besides short-lived but distressing discontinuation symptoms, interruptions in treatment have other risks. Chronicity may result when the underlying disorder is recurrently exacerbated by temporary discontinuation of treatment. Quality of life issues may have long-term consequences. For example, the effects of irritability and emotional absence can have a sustained adverse impact on family relationships and job performance. Patients sometimes miss work days because of discontinuation symptoms.

Discuss Alternative Treatments

A treatment plan should be described to patients either at the outset of treatment or as soon as improvement is noted. A plan provides patients with a clear picture of their illness and the available options for treating it. Dysthymic patients, in particular, need the reinforcement of a treatment plan. Because behavioral symptoms are often difficult to assess, specific symptoms should be targeted. The treatment plan should also include the expected duration of both an effective and an ineffective medication trial, the length of time to try a specific antidepressant dose, and the total intended duration of treatment including the continuation and maintenance phases. The plan should be concrete and presented in a way that is easily understood by the patient, which means tailoring the amount and complexity of information to the individual. It should be emphasized to the patient that antidepressants need to be tapered slowly to avoid possible discontinuation symptoms. Presenting a treatment plan is a particularly helpful approach for encouraging patients to accept the need for long-term treatment since, when patients are beginning to feel better, they sometimes stop taking medication and experience discontinuation symptoms that may be mistaken for a relapse.

Effective Communication

Compliance is increased when physicians convey empathy, support for, and understanding of the patient. One of the aims of the long-term Pittsburgh Study is to build an alliance between the health care providers including the office staff and the patient.[10] One strategy used by the researchers in this study was to characterize treatment of depression as an experiment that the patient and clinician undertake together. The ability of physicians, including primary care physicians, to establish rapport, assess patient attitudes and beliefs, and negotiate physician-patient differences in beliefs and expectations influences adherence to treatment, as does a hopeful attitude toward eventual recovery from depression.

Table 5 lists a variety of strategies to promote effective communication between the health care provider and the patient. They include expressing enthusiasm, establishing a therapeutic alliance, using a variety of channels of communication, providing the correct amount of information at a level that is appropriate for the individual patient, solicit-

ing questions from the patient, and making sure the patient is able and intends to take the medication as directed.

CONCLUSION

About 30% of patients discontinue treatment within the first month, and many more consistently skip doses. When medication is stopped suddenly or as few as two doses of an SRI with a shorter half-life, such as paroxetine, sertraline, or venlafaxine, are missed, there is a possibility that the patient will experience discontinuation symptoms. Physicians can help improve patient adherence to treatment—and concurrently reduce the risk of distressing discontinuation symptoms—by spending time educating patients about the nature of depression and its treatment, by providing a rationale for taking every medication dose, by making sure the patient understands that alternative treatments are available, and by establishing a therapeutic alliance with the patient. When physicians minimize noncompliance, patients are less likely to experience discontinuation symptoms that can affect their mental and physical health and that may have a sustained adverse impact on job performance and on family and social relationships.

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Discussion

Dr. Kaplan: In clinical practice, the behavioral symptoms of abrupt antidepressant discontinuation are often mistaken for relapse. A patient stops taking an antidepressant, becomes agitated or irritable, and these symptoms are misconstrued as a relapse of depressive symptoms.

Dr. Haddad: The discontinuation symptoms may be perpetuating poor compliance if they are unrecognized. Patients who experience symptoms after forgetting a few doses may think the drug is addictive and then refuse to take it. Clinicians who mistake discontinuation symptoms for signs of relapse may reinstate unnecessary long-term treatment.

Dr. Zajecka: I have seen patients who stop taking paroxetine for 48 hours and then experience sleep problems, agitation, anxiety, and flu-like symptoms. When patients report that they are anxious or not sleeping, particularly after they have initially responded to an antidepressant, the first question I ask is, "Have you missed or forgotten a dose?"

Dr. Kaplan: Patients sometimes stop taking their antidepressant without telling me. These are people who have had a beneficial clinical response and then, around Month 3 or 4, wonder, "What will happen if I stop? I think I am over this depression. I really don't need this medication any more." Because I initially educated them about the importance of continuing to take the antidepressant even after they begin to feel better, they don't inform me.

Other patients experience symptoms when they go away for 3 or 4 days without their antidepressant and miss several doses. Some take "drug holidays." I've had several patients experience discontinuation symptoms after they have tried drug holidays because they read about them in the popular press. The concept of drug holidays started in the psychiatric literature and filtered down to the lay press.

Dr. Zajecka: If a physician suggests that a patient take drug holidays to have sex, it might lead the patient to think, "If I could skip the antidepressant this weekend for sex, I could skip it next weekend for another reason." Giving patients a drug holiday conveys the wrong message, particularly when we look at the potential discontinuation symptoms these patients can have.

Dr. Young: Some patients stop taking antidepressants because the beneficial effects are delayed. When patients think of medicine, they think of antibiotics. When patients take antidepressants, the adverse effects come immediately and the beneficial effects come later. The patient may have difficulty resolving the issues in his or her mind.

Dr. Rosenbaum: I have found the telephone to be an enormously helpful tool for ensuring compliance. Patients who believe they can reach me by phone are less likely to quit taking their antidepressant.

Dr. Kaplan: Patients need to be told about the negative consequences of sudden discontinuation. We can reduce this problem of noncompliance by being good physicians and spending time with our patients. I find myself, particularly with patients who are taking paroxetine or venlafaxine, doing something I didn't do in the past. I say, "Make sure you do not stop this medication abruptly and you do not skip several doses because here is what could happen." When I educate my patients about the possibility of a discontinuation phenomenon, they become more compliant and are less likely to skip doses.

Clinical Management of Antidepressant Discontinuation

Jerrold F. Rosenbaum, M.D., and John Zajecka, M.D.

To minimize the symptoms of antidepressant discontinuation, gradual tapering is necessary for all serotonin reuptake inhibitors (SRIs) except fluoxetine, which has an extended half-life. Agents with shorter half-lives such as venlafaxine, fluvoxamine, and paroxetine should be tapered gradually. Discontinuation symptoms, which frequently emerge after abrupt discontinuation or intermittent noncompliance and, less frequently, during dose reduction, are generally mild, short-lived, and self-limiting but can be distressing and may lead to missed work days and decreased productivity. The symptoms may be somatic (e.g., dizziness and light-headedness; nausea and vomiting; fatigue, lethargy, myalgia, chills, and other flu-like symptoms; sensory and sleep disturbances) or psychological (anxiety and/or agitation, crying spells, irritability). Mild symptoms can often be treated by simply reassuring the patient that they are usually transient, but for more severe symptoms, it may be necessary to reinstitute the dosage of the original antidepressant and slow the rate of taper. Symptoms of discontinuation may be mistaken for physical illness or relapse into depression; misdiagnosing the symptoms may lead to unnecessary, costly tests and treatment. Thus, health care professionals need to be educated about the potential adverse effects of SRI discontinuation.

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Discontinuation symptoms occur in about one third of patients who stop serotonin reuptake inhibitor (SRI) therapy.[1] The most common symptoms are physical and may include feelings of disequilibrium (e.g., dizziness, light-headedness); nausea and vomiting; flu-like symptoms like fatigue, lethargy, myalgia, and chills; and sensory and sleep disturbances. However, psychological symptoms such as anxiety and agitation, crying spells, and irritability have also been noted.[2] Paying attention to the time frame of symptoms that emerge upon antidepressant discontinuation or when doses are missed will aid in the diagnosis of discontinuation symptoms. These symptoms usually commence within 24 to 72 hours of SRI discontinuation and last from 7 to 14 days. Reassurance is often the only treatment needed, but for cases where symptoms are particularly bothersome or severe, it may be necessary to reinstitute the antidepressant dose and slow the rate of taper. The risk of discontinuation events can be minimized by tapering all SRIs except for fluoxetine, which has an extended half-life.

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IMPORTANCE OF DIAGNOSIS

While treatment guidelines for depression provide advice on diagnosing depression, starting treatment, and establishing a maintenance regimen, little attention has been given to discontinuing treatment. As a result, few physicians are concerned with therapy termination, and many often fail to recognize and/or diagnose this cluster of symptoms as an antidepressant discontinuation event. Thus, the symptoms that accompany discontinuation are often either mistaken for the flu or a depressive relapse. Patients who experience discontinuation events are sometimes given costly, unnecessary diagnostic tests. For example, one patient with discontinuation dizziness was examined by a neurologist and otorhinolaryngologist, had magnetic resonance imaging of the head, and underwent tests for Lyme disease.[3] Other patients have been given complete physical examinations[4] or laboratory tests.[5] Psychiatric symptoms of discontinuation such as anxiety and agitation, crying spells, or irritability are also sometimes misdiagnosed as a depressive relapse and, as a result, the patient may resume antidepressant treatment for up to 1 year. Some patients who experience these psychiatric symptoms when they stop treatment or miss several doses of their antidepressant may become reluctant to continue treatment in the mistaken belief that they have become ad-

dicted to the antidepressant. Or, if the depression recurs several years later, they may not present for treatment because of the memory of adverse discontinuation events. Patients may also mistakenly conclude that symptoms of discontinuation are evidence of the need for continued treatment or continue with treatment to which they are only partially responsive because of adverse discontinuation events.

Untreated depression can be costly to society in terms of lowered productivity as well as increased morbidity and mortality. Although the symptoms of SRI discontinuation are seldom medically dangerous, they have an adverse effect on many patients' quality of life and have led to missed work days, lowered productivity, and higher medical costs. In one study,[6] 5 of 14 patients who discontinued fluvoxamine treatment took at least 1 day off from work, and 3 sought medical attention locally. Another patient was confined to bed and absent from work for 3 days because of severe dizziness associated with paroxetine discontinuation.[7] Frost and Lal[8] reported on two patients who had difficulty walking because of "electric shocks" and dizziness when paroxetine treatment was ended and one patient whose dizziness caused him to lose control of the steering wheel of his car after sertraline was stopped. Discontinuation events may also increase health care costs in terms of extra visits to physicians and hospital emergency rooms.

When patients present with new symptoms, particularly in an emergency room, they should be routinely asked if they have missed or forgotten to take any doses of medication, if the dosage has been changed recently, or if they have stopped taking any medication within the past several days. These questions are important for physicians in all specialties to ask, since, for example, an infant whose mother discontinued antidepressant treatment while breast-feeding experienced discontinuation symptoms.[9] Symptoms sometimes appear when patients miss several antidepressant doses, particularly of the shorter-acting SRIs such as paroxetine, sertraline, and venlafaxine for which discontinuation symptoms have been observed in as few as 12 to 24 hours after a missed dose.

Symptoms of antidepressant discontinuation can be differentiated from symptoms of depressive relapse by the time frame. Discontinuation-emergent symptoms usually begin within 1 to 3 days after antidepressant treatment is stopped, while signs of relapse are unlikely to become evident for 2 to 3 weeks. Withdrawal symptoms are unlikely to occur in patients who have been treated with SRIs for fewer than 7 weeks.[2] In addition, discontinuation events will remit within a couple of days after the antidepressant is reinstituted or one that is pharmacologically similar is substituted. Patients who have a history of antidepressant noncompliance, who have experienced discontinuation symptoms in the past, or who have treatment-emergent anxiety are at highest risk for experiencing discontinuation phenomena.

Table 1. Strategies to Manage Discontinuation Events

- Reassure the patient that the symptoms are likely to be short-lived and mild
- For acute symptoms, reinstitute the dosage and slow the rate of taper
- Gradually taper all serotonin reuptake inhibitors except fluoxetine
- Treat with agent with an extended half-life, e.g. fluoxetine

CLINICAL MANAGEMENT

Strategies to treat discontinuation symptoms are listed in Table 1. They include providing reassurance to the patient if symptoms are mild, slowing the rate of taper, and, for acute symptoms, reinstituting the antidepressant dosage or substituting another antidepressant that has a similar pharmacologic profile.

Provide Reassurance

Because discontinuation symptoms are usually mild and transient, many patients need only reassurance to help them cope with the adverse events. Results from studies on the contribution of cognitive-behavioral factors to the occurrence of discontinuation phenomena may lead to specific therapeutic interventions. For example, Otto et al.[10] found in a study of discontinuation of benzodiazepine patients that 76% of patients who received a combination of slow tapering and cognitive-behavioral therapy, as opposed to 25% of the group who received slow tapering alone, remained benzodiazepine-free at the 3-month follow up. The patients who received cognitive-behavioral therapy were informed about possible discontinuation symptoms and taught specific behaviors to cope with anxiety. The two groups experienced the same biological perturbations, but the group who had cognitive-behavioral therapy had their coping skills enhanced, which suggests that educational interventions can be helpful in successful antidepressant discontinuation. Often, it will be sufficient to tell the patient that the symptoms are likely to disappear within a few days.

Patients who have been responding well to SRI therapy and present with new symptoms such as dizziness and light-headedness, nausea and vomiting, sensory and sleep disturbances, flu-like symptoms, anxiety/agitation, crying spells, or irritability should be asked if they have forgotten or missed any doses. For example, they may have left their medication at home when they went on vacation. Since intermittent noncompliance can lead to discontinuation events, patients may need to be reminded frequently about the importance of taking every dose.

Slow the Rate of Taper

When a patient successfully completes treatment, the agents with shorter half-lives such as fluvoxamine, paroxetine, sertraline, and venlafaxine should be routinely tapered slowly to the minimum therapeutic dose or often

Table 2. Suggested Rate of Taper for SRIs After Successful Treatment*

SRI	Rate of Taper [a] (mg/d)	Minimum Therapeutic Dose (mg/d)	Usual Final Dose (mg/d)
Fluoxetine	...[b]	20	20
Fluvoxamine	50	100	25–50
Paroxetine	10	20	5–10
Sertraline	50	50	25–50
Venlafaxine[c]	25	75	25–50

*Abbreviation: SRI = serotonin reuptake inhibitor.
[a]Dose should be lowered every 5 to 7 days.
[b]Gradual taper generally unnecessary for fluoxetine.
[c]Manufacturer recommends taper for anyone who has been treated for ≥ 1 week.

below it (Table 2). The rate of taper should depend on a number of factors, including the pharmacologic profile of the specific drug, the current dose, and the duration of treatment. Paroxetine should be tapered slowly; the rate of taper should depend on the patient's comfort and discontinuation symptoms. The final dose may be below the minimum therapeutic dose. For example, a patient who has been taking 60 mg/day of paroxetine for 12 months should be tapered by 10 to 20 mg/week. If discontinuation symptoms appear while the patient is taking the recommended minimum therapeutic dose, it may be necessary to continue to half the dose until the patient is taking 5 mg/day. Similarly, it is often necessary for the final dose of fluvoxamine or sertraline to be lower than the starting dose.

Sometimes discontinuation symptoms persevere even if the SRI is being tapered slowly.[11,12] In that case, it may be necessary to reinstitute the original antidepressant dose and further slow the rate of taper. However, symptoms are occasionally so severe that patients are unable to discontinue antidepressant treatment.[13] If the symptoms continue, one additional strategy is to substitute fluoxetine, which has an extended half-life, for the original agent, as illustrated in one case in which the severe dizziness experienced by one patient after paroxetine discontinuation was alleviated when fluoxetine therapy was begun.[7]

Patients may also experience discontinuation symptoms when they are switched from one agent to another for lack of efficacy. Thus, the two drugs should be titrated, upward and downward, against the adverse effects. If the drugs have similar pharmacologic profiles, it is usually possible to reduce the dose of the initial drug quickly and simultaneously add the new medication.

FUTURE NEEDS

Guidelines for the treatment of depression should include advice on discontinuing SRI therapy. It is particularly important that information about the possibility of discontinuation reactions be included in patient educational materials designed for primary care physicians, who often treat depression. Medical students, psychologists, nurses, and pharmacists should also be aware that patients may experience discontinuation symptoms when they stop SRI treatment since patients often bring complaints to these nonphysicians.

Patient education should be provided by physicians and other mental health professionals. When antidepressant treatment is begun or shortly after the patient has started to respond to an antidepressant, he or she should be educated about the importance of taking every dose and about the risk of discontinuation symptoms if treatment is stopped abruptly or interrupted regularly.

Additional clinical strategies to treat antidepressant discontinuation events may become evident after more data is gathered about the phenomenon. For example, little research has been published on the percentage of paroxetine-, sertraline-, or venlafaxine-treated patients who experience discontinuation reactions. Ideally, every antidepressant should be included in a double-blind, placebo-controlled study of discontinuation events as part of the phase 3 evaluations during the Food and Drug Administration (FDA) approval process. Basic studies are also necessary to establish the mechanism of action of the discontinuation phenomena and the specific risk factors for discontinuation symptoms. In addition, specific groups such as the young or the elderly or patients who become anxious or nauseated when they start therapy should be studied to ascertain whether they may be at greater risk for suffering through a discontinuation reaction.

CONCLUSION

When initiating antidepressant therapy for a patient, a physician must consider the eventual risk of a discontinuation syndrome. While patients may experience discontinuation reactions when they stop therapy with any SRI, discontinuation-emergent symptoms have been reported much less frequently for fluoxetine than the short half-life SRIs, paroxetine, sertraline, fluvoxamine, and venlafaxine. Patients who are discontinuing therapy need to be tapered gradually from all SRIs except fluoxetine; sometimes the final dose will be lower than the minimum therapeutic dose. The extended half-life of fluoxetine may provide protection against discontinuation symptoms, and patients who are unable to tolerate these discontinuation events may benefit from a switch to fluoxetine.

Drug names: fluoxetine (Prozac), fluvoxamine (Luvox), paroxetine (Paxil), sertraline (Zoloft), venlafaxine (Effexor)

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Discussion

Dr. Haddad: Physicians routinely ask patients to list the medications they are taking, but, when someone presents with acute symptoms, the physician seldom asks, "Are there any medications that you have stopped taking in the last few days?" That question should also be routine.

Dr. Schatzberg: The immediate drug history is extremely important. It should include changes in medication as well as those that have been discontinued. We don't teach residents—particularly those who are working in emergency rooms—to ask these questions.

Dr. Rosenbaum: For example, in August a patient was hospitalized at my medical center to rule out a myocardial infarction. It turned out that the symptoms occurred in the context of venlafaxine discontinuation. When venlafaxine was reintroduced, the symptoms abated. The patient was ultimately switched to fluoxetine.

Dr. Young: Serotonin selective reuptake inhibitors (SSRIs) are the first-line treatment for premenstrual dysphoric disorder (PMDD), but many women want to discontinue taking medication during certain parts of the menstrual cycle. Thus, my colleagues and I tend to prescribe fluoxetine for PMDD because it is more robust during discontinuation.

Dr. Haddad: Discontinuation symptoms are often misdiagnosed. Einbinder [Am J Psychiatry 1995;152:1235] described a young woman who was sent to a neurologist and an otorhinolaryngologist, had magnetic resonance imaging of her head, and was tested for Lyme disease because of dizziness that occurred in the context of SSRI discontinuation. Some patients miss a few doses and then drop out of treatment when they experience discontinuation symptoms. Symptoms develop in other patients when the antidepressant is stopped abruptly at the end of treatment. When depression recurs several years later, the patient is unwilling to begin treatment because the discontinuation phenomena after the first episode were unpleasant.

Dr. Young: To avoid discontinuation symptoms, my colleagues and I educate the patients about possible symptoms and reassure them when the symptoms occur that they will be short-lived. We titrate the dose down against the discontinuation syndrome. The rate of titration depends on the pharmacologic characteristics of the drug. Thus, paroxetine is titrated more gradually than fluoxetine.

Dr. Schatzberg: I decrease the paroxetine dose about 10 mg/day every 5 to 7 days.

Dr. Young: The crucial period is at the end when patients are taking 10 mg/day of paroxetine. I tend to decrease the paroxetine dose to 5 mg/day.

Dr. Haddad: The SSRIs, except for paroxetine, can usually be discontinued when the patient is taking the minimum therapeutic dose, but the daily paroxetine dose needs to be tapered to below 20 mg, i.e., the smallest tablet that the manufacturer makes.

Dr. Kaplan: Some patients have discontinuation symptoms when they stop the minimum therapeutic dose of sertraline or fluvoxamine.

Dr. Young: Any condition that makes long-term patient compliance less likely is something that has profound pharmacoeconomic costs and costs in terms of human suffering.