Discontinuation Symptoms After Treatment With Serotonin Reuptake Inhibitors: A Literature Review

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Background: The discontinuation of many pharmacologic agents is associated with characteristic withdrawal symptoms. Antidepressants, particularly the tricyclic antidepressants (TCAs), are known to be associated with a group of common symptoms upon discontinuation. Serotonin reuptake inhibitors (SRIs) are also taking their respective place in the literature with reports of discontinuation symptoms. This review summarizes case reports and reports that allow systematic assessment of discontinuation symptoms following SRI discontinuation.

Method: A computerized literature search was conducted using a MEDLINE search to identify reports of withdrawal effects following discontinuation of SRIs. Additional reports were found in the bibliographies of various published reports.

Results: SRI discontinuation symptoms in adults are summarized in 24 case reports and 9 reports from controlled clinical trials. Additionally, 3 case reports addressing SRI discontinuation in the neonate are described. The reports describe clusters of symptoms commonly associated with the discontinuation of an SRI.

Conclusion: We propose to define an antidepressant discontinuation syndrome as the onset of a cluster of somatic and psychic symptoms following the discontinuation of an SRI and not attributable to other causes (e.g., concomitant medication, illness). These symptoms include dizziness, light-headedness, insomnia, fatigue, anxiety/agitation, nausea, headache, and sensory disturbance. The syndrome may last up to 3 weeks and may be improved by restarting the antidepressant or starting an antidepressant with a similar pharmacologic profile.

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The discontinuation of many pharmacologic agents is associated with characteristic withdrawal symptoms. Antidepressants, particularly the tricyclic antidepressants (TCAs), are known to be associated with a group of common symptoms upon discontinuation. Symptoms that may result after either abrupt or gradual discontinuation of TCAs are described extensively in the literature[1,2] and include (1) gastrointestinal and/or other general (somatic) medical symptoms with or without anxiety and agitation, e.g., vomiting, nausea, diarrhea, headache, fatigue, and malaise; (2) sleep abnormalities, including initial and middle insomnia, increased dreaming, and vivid dreams; (3) akathisia and parkinsonism; and/or (4) paradoxical behavioral activation resulting in hypomanic/manic symptoms. While symptoms may occur as early as 12 hours after a missed TCA dose, withdrawal phenomena characteristically develop 24 to 48 hours after the last dose. Symptoms of TCA discontinuation have been reported to last as long as 1 month.[1]

To avoid potential withdrawal symptoms, gradual tapering of TCAs over at least a 4-week period is recommended. Persistent withdrawal symptoms may be treated by reinstitution of the TCA with a subsequent slower taper and/or treatment with an anticholinergic agent.[2] The pathophysiology underlying TCA withdrawal phenomena is hypothesized to involve cholinergic system supersensitivity.[1] Additionally, an interaction of the cholinergic and monoaminergic systems may play an important role in the development of some withdrawal phenomena, e.g., manic-like symptomatology.[3]

With the advent of fluoxetine and bupropion in the 1980s, it appeared as though the antidepressant withdrawal phenomena were associated only with TCAs. Furthermore, the cholinergic rebound theory was supported since these newer agents lacked clinically significant anticholinergic effects. As a result, little attention was paid to the need to taper these newer agents or to be cognizant of potential withdrawal symptoms.

As we will review in this paper, increasing reports of antidepressant withdrawal symptoms similar to those associated with TCAs have surfaced in the literature with the recent development and widespread use of the short half-life serotonin reuptake inhibitors (SRIs) paroxetine,

sertraline, fluvoxamine, and venlafaxine. Reports have also appeared on withdrawal effects after discontinuation of fluoxetine. Additionally, the Internet has become a venue for exchange of anecdotal reports of antidepressant withdrawal symptoms such as "flashes in my peripheral vision and headaches,"[4] "random flashes of split-second dizziness . . . like a mild electrical jolt in your brain,"[4] and "electric shock phenomena."[5]

For the clinician, it is important to be aware of potential antidepressant withdrawal symptoms since they may occur in several ways: after routine discontinuation of treatment, after switching antidepressant treatments, or, in the patient who is noncompliant with treatment, after missing antidepressant doses. Withdrawal symptoms should be distinguished from a relapse or worsening of symptoms of the underlying illness and also from side effects of the medication, which could otherwise result in premature discontinuation of the antidepressant. Furthermore, new onset of symptoms in a patient recently switched from one antidepressant to another may be the result of side effects of the new medication, drug interactions, and/or discontinuation symptoms from the discontinued antidepressant.

We reviewed the literature describing symptoms after SRI discontinuation to identify symptom clusters, including their onset and duration, in an effort to propose a definition of an SRI discontinuation syndrome that may be applicable to many antidepressant subtypes, including those previously described with TCAs, and that may identify a possible mechanism underlying this phenomenon.

METHOD

A computerized literature search was conducted using MEDLINE to identify reports describing withdrawal symptoms arising from discontinuation of SRIs. We also utilized personal communications and searches by hand through various journals. Few reports in the literature examine SRI discontinuation in controlled samples where the emergence of discontinuation symptoms can be systematically assessed.

RESULTS

Anecdotal Case Reports

A summary of case reports of SRI withdrawal phenomena is represented in Table 1.

Numerous case reports describe withdrawal symptoms in patients after discontinuing treatment with paroxetine[6–11] and sertraline.[6,10,12,13] There are fewer reports regarding venlafaxine,[14] fluvoxamine,[15] or fluoxetine.[16–18] As seen in Table 1, a diverse range of symptoms is reported following paroxetine discontinuation. Dizziness/vertigo, nausea, and fatigue/malaise are the most commonly reported. Patients also reported gastrointestinal symptoms, such as vomiting and abdominal discomfort, agitation, insomnia, myalgias, tremulousness/tremors, "electric sensations," headaches, vivid dreams, and other miscellaneous symptoms. Sertraline discontinuation has been associated with fatigue/malaise, headaches, incoordination, as well as dizziness/vertigo, gastrointestinal symptoms, and paresthesias. Fewer symptoms have been reported for fluoxetine; dizziness/vertigo was most frequently reported.

An additional brief comment in the literature describes a "withdrawal buzz" consisting of an intense, distracting sensation within the head and possible brief disorientation or dizziness after withdrawal of either paroxetine, sertraline, or fluoxetine.[19]

Reports From Controlled Clinical Trials

Reports of withdrawal phenomena were also reported within the text of nine clinical trials. In these studies, patients were treated with SRIs including paroxetine, fluvoxamine, and venlafaxine for disorders including depression, obsessive-compulsive disorder (OCD), anxiety disorders, and stuttering. Only one paper was published comparing the frequency of withdrawal symptoms among SRI antidepressants.[20]

In that retrospective chart review, 171 patients were followed after discontinuation from either clomipramine, paroxetine, fluvoxamine, sertraline, or fluoxetine.[19] Patients who reported at least one qualitatively new symptom were considered as cases. Patients were followed for at least 2 weeks after discontinuation of paroxetine, fluvoxamine, and clomipramine and for at least 4 weeks after the last dose of sertraline or fluoxetine. Twenty-one patients (12.3%) qualified as cases having withdrawal symptoms from the above SRIs with the exception of fluoxetine, which had no reports of discontinuation symptoms in this case series. The most frequently reported symptom was dizziness, followed by lethargy, paresthesia, nausea, vivid dreams, irritability, and lowered mood. Symptoms occurred within 5 days of discontinuation regardless of taper and lasted up to 21 days. Of the 93 patients treated with the short half-life SRIs (paroxetine or fluvoxamine), 17.2% reported symptoms. This finding is in striking contrast to patients treated with long half-life agents: 1 (2.2%) of 45 patients in the sertraline group and none in the fluoxetine group reported new onset of symptoms after drug discontinuation. Consistent with previous reporting of TCA withdrawal, this review reported discontinuation symptoms in 4 (30.8%) of 13 patients after clomipramine treatment.

Paroxetine. Withdrawal symptoms were monitored in two separate studies examining the efficacy of paroxetine in the treatment of OCD. Barr et al.[21] observed withdrawal symptoms after paroxetine treatment in six patients who participated in a 12-week, placebo-controlled, double-blind OCD study. At the conclusion of the study, patients were offered open-label treatment with paroxetine. After 12 weeks of treatment, the six patients were

Table 1. Case Reports: Serotonin Reuptake Inhibitor Discontinuation Syndrome*

Case Report	Gender	Age (y)	Diagnosis	Dose (mg/d)	Duration (mo)	Taper	Symptom Onset (d)	Symptom Duration (d)	Symptoms: Dizziness/Vertigo	Incoordination	Myalgias	Fatigue/Malaise	GI Symptoms	Nausea	Vomiting	Insomnia	Headache	Agitation	Tremulousness	Electric Sensations	Abnormal Dreams	Chills	Other
Paroxetine																							
Fava and Grandi, 1995[6]	M	43	MDD	40	3	Yes	7	10	✓	✓	✓	✓	…	…	…	…	…	…	…	✓	…	…	Hypnagogic visual hallucinations
	F	22	SAD	40	?	No	10	7	…	…	✓	…	…	✓	✓	✓	…	…	…	…	…	…	…
	F	25	MDD	20	4	?	7	10	…	…	✓	✓	…	…	…	✓	…	✓	…	…	…	…	Rhinorrhea
Pyke, 1995[7]	F	44	GAD	20	3	?	3	23	✓	…	…	…	✓	✓	…	…	…	…	…	…	…	✓	Anorexia, eye movement abnormalities
Phillips, 1995[8]	F	40	?	20	1–2	No	3	?	…	…	…	…	✓	✓	✓	…	✓	✓	…	…	…	…	…
DeBattista and Schatzberg, 1995[9]	M	26	MDD	10	3	No	2	RM	✓	…	…	✓	…	✓	…	…	…	…	…	…	…	…	…
	M	46	BAD	10	?	No	1	RM	…	…	…	…	…	…	✓	…	✓	…	✓	…	…	…	…
Frost and Lal, 1995[10]	M	32	OCD	20	2	Yes	2	140	…	…	…	…	…	…	…	…	…	…	…	✓	…	…	…
	M	28	PD	30	2	Yes	2	7–21	✓	…	…	…	…	✓	…	✓	…	…	✓	✓	…	…	…
Dominguez and Goodnick, 1995[11]	F	37	MDD	40	3	?	3	RM	✓	…	…	…	…	…	…	…	…	…	✓	✓	✓	…	…
	F	26	OCD	40	2.5	?	2	RM	✓	…	…	…	…	…	…	✓	…	…	…	…	✓	…	Crying spells, depersonalization, increased appetite
	F	48	OCD, MDD	40	6	?	3	RM	✓	…	…	✓	✓	✓	…	…	…	…	…	…	✓	…	Crying spells, poor concentration
Sertraline																							
Fava and Grandi, 1995[6]	F	27	MDD	50	6	?	5	7	✓	✓	✓	✓	…	…	…	…	✓	…	…	…	…	…	…
Frost and Lal, 1995[10]	M	22	MDD	150	5	Yes	1	91	…	…	…	…	…	…	…	…	…	…	…	✓	…	…	…
Louie et al, 1994[12]	F	46	Mixed anxiety-depression	100–150	2.1	Yes	2	RM	…	…	✓	✓	✓	…	…	✓	✓	…	…	…	✓	✓	Sore eyes, shortness of breath, impaired short-term memory
Leiter et al, 1995[13]	F	37	MDD	100	8	Yes	2	31	…	✓	…	✓	…	…	…	…	✓	…	…	…	…	…	Irritability, slowed thinking/ decreased concentration, feeling detached, paresthesias
	M	33	MDD	100–150	9	Yes	1	14	✓	✓	…	…	✓	✓	…	…	…	…	…	…	…	…	Ringing in ears, fever, paresthesias
Fluoxetine																							
Berlin, 1996[16]	M	36	GAD, DYS	20–40	15	?	2	46	✓	…	…	…	…	…	…	…	…	…	…	…	…	…	Irritibility, lability
	M	34	MDD	20	8.5	Yes	7	56	✓	…	…	…	…	…	…	…	…	…	…	…	…	…	…
	M	52	MDD	20	2.5	?	25	28	✓	…	…	…	…	…	…	…	…	…	…	…	…	…	Imbalance the patient could “almost hear”
Einbinder, 1995[17]	F	?	MDD	20–40	3	No	3	RM	…	…	…	✓	…	…	…	…	…	…	…	…	…	…	…
	(Same patient)			40	2	Yes	9	3	✓	…	…	…	…	…	…	…	…	…	…	…	…	…	Eye twitch
Stoukides and Stoukides, 1991[18]	M	32	MDD	?	6	No	1	?	…	…	…	…	…	…	…	…	…	✓	…	…	…	…	Dystonia, high blood pressure, diaphoresis, tachycardia, increased temperature
Venlafaxine																							
Farah and Lauer, 1996[14]	F	32	MDD	300	8	No	1.5	< 1 d	…	…	…	✓	✓	✓	…	…	✓	…	…	…	…	…	Tinnitus, sinus congestion
Fluvoxamine																							
Szabadi, 1992[15]	F	30	OCD	100–150	12+	No	1	?	✓	…	…	…	…	…	…	…	…	…	…	…	…	…	Hypomanic symptoms, aggression

*Abbreviations: ? = unknown, BAD = bipolar affective disorder, DYS = dysthymia, GAD = generalized anxiety disorder, GI = gastrointestinal, MDD = major depressive disorder, OCD = obsessive-compulsive disorder, PD = panic disorder, RM = restarted medication, SAD = seasonal affective disorder.

tapered over a 1- to 2-week period from a dose of 60 mg/day. Three of the six patients experienced new adverse effects within 3 to 7 days after drug discontinuation. Symptoms lasted 1 week and included vertigo, nausea, emesis, diarrhea, gait instability, myalgias, fatigue, insomnia, rhinorrhea, and visual phenomena.

Paroxetine withdrawal symptoms were described in 5 of 13 patients who participated in the medication group in a placebo-controlled OCD study.[22] All patients were treated for an unspecified time with 60 mg/day (except for one patient on 40 mg/day). Four of the 5 patients were tapered over 10 to 23 days; patients reported discontinuation symptoms occurring within 3 to 10 days and persisting up to 2 weeks. Dizziness and/or light-headedness were cited in all patients, and 1 patient also had nausea, paresthesias, and headaches.

A third report[23] cites evidence of withdrawal symptoms in two patients involved in a double-blind, placebo-controlled clinical trial of paroxetine for the treatment of stuttering. After 6 weeks of treatment with paroxetine (50 mg/day), the patients entered a 2-week placebo period. Paroxetine was abruptly discontinued in one patient and gradually tapered over 12 days in the second patient. Both patients experienced a biphasic symptom pattern of initial hypomanic-like symptoms followed by aggressiveness and suicidal impulsivity. Physical symptoms in one patient consisted of dizziness, blurred vision, nausea, lethargy, and insomnia. Symptoms abated within 1.5 to 2.5 weeks.

Oehrberg et al.[24] cited evidence of withdrawal symptoms in a randomized, double-blind, placebo-controlled study of paroxetine in the treatment of panic disorder. Nineteen (34.5%) of 55 patients experienced withdrawal effects after discontinuing paroxetine as compared with 7 (13.5%) of 52 patients discontinuing from placebo. Most patients reported one symptom, with the most frequently reported symptom being dizziness.

As reported by Choo,[25] the Committee on Safety of Medicines in the United Kingdom indicated that withdrawal symptoms appear to be more frequent after discontinuation of paroxetine, compared with sertraline and fluoxetine. The Physicians' Desk Reference (PDR)[26] documents postmarketing reports of symptoms associated with abrupt discontinuation of paroxetine, including dizziness, sensory disturbances, agitation or anxiety, nausea, and sweating.

Fluvoxamine. Two reports address withdrawal symptoms after discontinuation of treatment with fluvoxamine in patients with anxiety disorders. Mallya et al.[27] used the 90-item Hopkins Symptom Checklist and a subjective distress questionnaire to retrospectively assess possible withdrawal symptoms in 17 patients who participated in a double-blind, placebo-controlled study examining the treatment of OCD with fluvoxamine. After a 1-year open-label treatment continuation, patients were tapered off fluvoxamine from dosages of between 100 to 300 mg/day over a variable number of weeks. Twenty-four percent (N = 4) of the participants reported onset of new symptoms after initiation of the taper. Two patients reported dizziness, and 2 others experienced dizziness as well as nausea, headache, confusion, memory problems, low energy, and weakness.

Another report documenting discontinuation symptoms after fluvoxamine treatment[28] describes 14 patients who participated in a multicenter double-blind study examining fluvoxamine versus placebo in the treatment of panic disorder. In a 6-month, open-label extension, the 14 patients received a mean dose of 236 mg/day (range, 100–300) of fluvoxamine for a duration of 7 to 8 months. Telephone assessments occurred on postwithdrawal Days 5 and 10, and a clinic assessment was performed 2 weeks after discontinuation. Patients were not prompted during the assessments, but were asked to report new or ongoing symptoms. Eighty-six percent (N = 12) of the patients reported new symptoms after fluvoxamine discontinuation, including dizziness/incoordination, headaches, irritability, and nausea. Symptoms began as early as 24 hours after discontinuation of medication; they were reported most frequently on Day 5, with subsequent diminution of symptoms by Day 14. Intensity was assessed on a scale of 1–3 (3 indicates severe symptoms). Symptoms with a score greater than 2 were irritability, poor concentration, sleep disturbance, headache, nausea, tinnitus, agitation, and depression. Severity of these symptoms peaked at Day 5; for some of the patients, these symptoms were associated with significant impaired function (e.g., 5 patients took a day off from work).

Venlafaxine. In a 12-week, open-label trial of venlafaxine[29] for the treatment of OCD, patients were treated with a mean dose of 308 mg/day (range, 150–375) followed by a 4- to 14-day taper. Four of nine patients experienced, within an unspecified time, a flu-like syndrome with muscle aches, fatigue, headache, nausea, and dizziness. Withdrawal symptoms associated with discontinuation of treatment were relieved in three of the cases by resuming venlafaxine and then following with a more gradual taper. The fourth patient experienced symptoms despite the initiation of fluoxetine.

A retrospective analysis of discontinuation symptoms revealed a cluster of symptoms that occurred at an incidence of at least 5%, which was at least twice the placebo incidence. These symptoms included asthenia, dizziness, headache, insomnia, nausea, and nervousness.[26]

Fluoxetine. As suggested from the case reports in Table 1, discontinuation of fluoxetine appears to result in fewer symptoms reported compared with other SRIs. Kreider et al.[30] assessed the tolerability of switching from fluoxetine to paroxetine either immediately after discontinuing fluoxetine or after a 2-week placebo period in patients diagnosed with major depression. Patients that had been treated for a minimum of 6 weeks with fluoxetine

(approximately 70% on 20 mg/day; range, 10–80) were entered into the study. Newly reported symptoms during the 2-week washout period were compared between the two treatment groups. The profile of adverse experiences during the first 2 weeks of the trial was similar in the immediate-switch group and placebo washout group. These data are ambiguous because baseline adverse effects were not assessed. Therefore, it is unclear whether the adverse effects reported were secondary to starting paroxetine, to stopping fluoxetine, or to the reemergence of depressive symptoms.

Special Populations

In addition to adults, other clinically important populations may be vulnerable to withdrawal symptoms after discontinuation of SRIs. Kent and Laidlaw[31] describe neonatal withdrawal symptoms after cessation of breastfeeding in a 3-week-old infant whose mother had been on 200 mg/day of sertraline throughout pregnancy. Within 1 day, the baby experienced agitation, restlessness, poor feeding and sleep patterns, constant crying, and enhanced startle reaction; these symptoms persisted for a few days. In contrast, no evidence of withdrawal symptoms was observed after breastfeeding was stopped in a 1.5-week-old infant whose mother was on 150 mg/day of sertraline.[32] Goldstein[33] followed 115 infants whose mothers had been taking fluoxetine during the third trimester of pregnancy. Mild and transitory postnatal complications were observed in 13% of these infants. These included jitteriness, irritability, sleep disturbance, heart palpitations, and hyperbilirubinemia, among others. While there was no clear evidence of a withdrawal syndrome in this population, larger studies are warranted to further investigate this notion.

In children and adolescents, marked, uncharacteristic irritability and argumentativeness have been observed after abrupt discontinuation of SRIs, particularly with sertraline[5] (Johnson M. Oral communication. October 1996.)

DISCUSSION

Summary

Withdrawal symptoms associated with the discontinuation of serotonin reuptake inhibitors are similar to those previously reported with TCAs. Paroxetine, fluvoxamine, and venlafaxine, compared with fluoxetine and sertraline, may be associated with more frequent reporting of adverse discontinuation symptoms and a greater number of reported discontinuation symptoms per patient. Symptoms may occur earlier after discontinuation of paroxetine, sertraline, fluvoxamine, and venlafaxine than with fluoxetine. While these trends are noted among the SRIs, the reports must be interpreted with caution. We focus on SRIs that have been on the market longer (perhaps explaining the increased number of reports involving paroxetine in comparison to the newer agents). Physicians should also be alert to the potential of discontinuation effects with the novel agents such as nefazodone, bupropion sustained release, and mirtazapine. (To date, these agents have not been reported in the literature to be associated with discontinuation symptoms.)

Well-controlled comparison studies have not been reported to date. These reports are limited by the lack of consistent control over important variables, i.e., concomitant medications, psychiatric diagnosis, the duration and effect of treatment prior to discontinuation, and either abrupt or gradual discontinuation. Furthermore, these findings are restricted by the lack of uniformity of describing how the symptoms were observed, collected, and reported. Despite such limitations, the constellation of these reports is consistent with those observed in our clinical experience.

Hypothetical Basis of SRI Discontinuation Syndrome

We propose a hypothesis of the pathophysiologic basis of SRI discontinuation syndrome. One common factor among the antidepressants associated with discontinuation symptoms is that they block the presynaptic reuptake of serotonin. Theoretically, the reuptake blockade of serotonin is thought to result, over time, in the down-regulation (or desensitization) of postsynaptic serotonin and norepinephrine receptors. Reversal of serotonin reuptake blockade may result in a restoration or possible acute enhancement of serotonin reuptake activity upon discontinuation of the antidepressant, resulting in acute depletion of synaptic serotonin. The reduced availability of serotonin to the already desensitized postsynaptic receptors may produce a hyposerotonergic state.

This hypothesis is supported by a theory proposed by some authors[15,34] suggesting that withdrawal of SRIs results from a relative deficiency of serotonin. Furthermore, it is possible that the hyposerotonergic state may have direct or indirect effects on neurotransmitter systems (such as serotonin, norepinephrine, dopamine, acetylcholine, or gamma-aminobutyric acid systems), resulting in a variety of clinical symptoms. The readaptation of these neurotransmitter systems should, theoretically, occur over a period of 2 to 3 weeks, which correlates with improvement of withdrawal symptoms. Other potential mechanisms may also be hypothesized, such as readaptation of 5-HT_{1A} and 5-HT_2 receptors. While the symptoms appear to be time-limited, we know little about adaptive CNS physiologic changes that may occur as a result of short-term or long-term exposure to centrally acting psychotropic agents.[35] Some have postulated a phenomenon of sensitization of neurobiological processes, akin to the concept of tolerance, as a possible consequence of antidepressant treatment.[36]

Differences among antidepressants in the onset, frequency, and intensity of withdrawal symptoms may be further explained by each drug's individual pharmacokinetic and pharmacologic profile. The short half-life SRIs appear

to be more commonly associated with acute discontinuation symptoms compared with longer half-life agents. Abrupt discontinuation of short half-life drugs may be more likely to promote the appearance of discontinuation symptoms as compared with a gradual taper. One of the factors associated with antidepressant discontinuation symptoms may be a cholinergic rebound, as described with TCAs. The greater anticholinergic effect of paroxetine relative to the other SRIs, and comparable to some TCAs, may account, in part, for the relative frequency of discontinuation symptoms with paroxetine. However, Fava and Grandi[6] propose that the cholinergic rebound effect may not be sufficient to explain antidepressant discontinuation symptoms as paroxetine discontinuation symptoms were not reversed with desipramine treatment. The greater potency of paroxetine in blocking the reuptake of serotonin, relative to the other SRIs, may also be important in the development of SRI discontinuation symptoms.

SRI Discontinuation Syndrome and Treatment

We propose to define an antidepressant discontinuation syndrome as the onset of a cluster of somatic and psychic symptoms after the discontinuation of an antidepressant drug, not attributable to other causes (e.g., concomitant medication, illness). Symptoms have been reported following abrupt discontinuation and during taper as well as after gradual dose reduction. These symptoms include dizziness, light-headedness, insomnia, fatigue, anxiety/agitation, nausea, headache, and sensory disturbance. Other, less commonly reported symptoms may include hypomanic-like symptoms, worsening of mood, aggressiveness, and suicidality. The syndrome may last up to 3 weeks and may be improved by restarting the antidepressant or starting an antidepressant with a similar pharmacologic profile. While the reports described above do not imply causality, the cluster of symptoms that comprise SRI discontinuation syndrome, including their onset and duration, are probably a function of individual pharmacologic and pharmacokinetic factors of the various agents.

The clinician needs to be aware of potential symptoms associated with an antidepressant discontinuation syndrome in a patient treated with antidepressants, either during treatment (as a result of missed doses and/or noncompliance) or when stopping treatment. The cluster of symptoms associated with the syndrome should alert the clinician to potential noncompliance in an otherwise adequately treated patient. Abrupt discontinuation, including "drug holidays," of those antidepressants commonly associated with antidepressant discontinuation syndrome should be avoided in susceptible individuals, and doses should be tapered over time. Interrupting or stopping SRIs may also contribute to possible deleterious effects on the course of illness.[35,36] Similar to suggestions made regarding discontinuation with TCAs, we recommend that patients be tapered from their SRIs rather than abruptly discontinued if clinically indicated. If discontinuation symptoms surface during the course of an SRI taper, the clinician should consider decreasing the rate of the taper. Tapering should be tailored to the individual patient and to the specific agent(s) being used as well as to any subsequent treatments introduced.

While numerous case reports describe discontinuation phenomena after discontinuation of SRIs, scant literature is available that examines the possible drug-related differences in these syndromes. Percentages of patients reporting SRI discontinuation syndrome range from 5%[19] to 86%.[28] Future research might (1) clearly identify the risk of adverse reactions after abrupt discontinuation or tapering of SRIs, (2) delineate the possible drug-related differences between the various SRI discontinuation syndromes, and (3) provide recommendations for stopping medication and for switching from one antidepressant to another in order to minimize such symptoms.

Drug names: bupropion (Wellbutrin), clomipramine (Anafranil), desipramine (Norpramin and others), fluoxetine (Prozac), fluvoxamine (Luvox), nefazodone (Serzone), paroxetine (Paxil), sertraline (Zoloft), venlafaxine (Effexor).

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