Prospective Studies of Adverse Events Related to Antidepressant Discontinuation

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The value of a prospective assessment of discontinuation-emergent symptoms proximal to the termination of antidepressant treatment cannot be overstated. Though varying in frequency and intensity, nearly all classes of antidepressants have been linked with discontinuation reactions and the associated psychological, physical, and somatic discomfort. Spontaneous reports have been typically used to gauge the risks of discontinuation reactions. Judging from a number of prospective studies, spontaneous reports very likely underestimate the occurrence of discontinuation reactions. This probability suggests that systematic inquiry must urgently become a part of the assessment in antidepressant discontinuation studies. Insight into the number and type of events that may occur following antidepressant discontinuation may be gleaned from instruments such as the Discontinuation-Emergent Signs and Symptoms Scale. This article takes a comprehensive view of a number of studies dealing with discontinuation-related adverse events. It discusses key issues in the analysis of incidence rates of antidepressant discontinuation–emergent adverse events such as the obvious bias of both clinicians' and patients' being aware of the treatment discontinuation. This article also looks at early prospective studies of antidepressant discontinuation reactions based on spontaneous reports and discusses, while making the case for, prospective studies based on systematic inquiry.

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Over the past 50 years, there have been a number of anecdotal reports in the literature of the emergence of psychological and somatic symptoms following discontinuation of a number of antidepressants, including tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs), and serotonin-norepinephrine reuptake inhibitors (SNRIs).[1] There have also been numerous attempts to assess the incidence rates of discontinuation reactions associated with the use of specific antidepressants. For example, the pooled estimated rate of discontinuation reactions from 7 studies with TCAs alone was 42.5% of 235 patients.[1] This estimate, however, was generated from uncontrolled studies that did not include a placebo comparison with control for the natural fluctuation of psychological and somatic symptoms among psychiatric patients. With MAOIs, the rate of discontinuation reactions reported with phenelzine (32.2%) appeared to be similar to that of TCAs (29.4%) within a single study.[2] With SSRIs, agents with relatively shorter half-lives, such as fluvoxamine and paroxetine, have been associated with rates of discontinuation reactions of approximately 50%,[3–6] while SSRIs with relatively longer half-lives, such as sertraline and fluoxetine, tended to have significantly lower rates of discontinuation reactions, according to a retrospective chart review of 352 patients treated with SSRIs or clomipramine.[7]

CHARACTERISTICS OF ANTIDEPRESSANT DISCONTINUATION–EMERGENT ADVERSE EVENTS

Literature reviews[1,8–10] have suggested that a broad range of somatic symptoms may emerge following antidepressant treatment discontinuation. The most commonly reported somatic symptoms include headaches, dizziness, light-headedness, diminished appetite, fatigue, sweating, tremors, chills, sensory disturbances (paresthesias and tremors), sleep disturbances (vivid dreams and insomnia), somnolence, flulike symptoms, and gastrointestinal physical symptoms (nausea and vomiting). Other, less common somatic symptoms include electric-like shocks, myalgias, parkinsonism, arthralgias, and balance difficulties, and, with TCAs, cardiac arrhythmias.

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The same literature reviews[1,8–10] have suggested that, following antidepressant treatment discontinuation, a number of psychological symptoms may emerge, such as agitation, anxiety, akathisia, panic attacks, irritability, aggressiveness, worsening of mood, dysphoria, crying spells or mood lability, overactivity or hyperactivity, depersonalization, decreased concentration, slowed thinking, confusion, and memory/concentration difficulties. In patients with a bipolar diathesis, it is not uncommon to observe hypomania or mania upon antidepressant discontinuation.[8] It appears that patients who experience reactions following antidepressant discontinuations tend to experience both psychological and somatic symptoms, and, at least anecdotally, it is uncommon to observe patients with only somatic or psychological symptoms.

The course of these discontinuation reactions with antidepressants of either short or intermediate half-lives is quite typical, in that symptoms tend to emerge within 2 to 5 days from treatment discontinuation, and they last usually 7 to 14 days.[1,9,10] Antidepressants with relatively shorter half-lives, longer duration of antidepressant treatment, and abrupt discontinuations of the antidepressant have been considered the primary risk factors for these reactions.[1,9] With antidepressants with relatively shorter half-lives, it is not uncommon to observe the emergence of discontinuation symptoms even when the drug is being tapered, particularly when the dose reduction is rapid.[11]

ISSUES IN THE ASSESSMENT OF INCIDENCE RATES OF ANTIDEPRESSANT DISCONTINUATION–EMERGENT ADVERSE EVENTS

Several methodological approaches have been used to determine the likelihood of experiencing discontinuation reactions with antidepressants. A common method involves the retrospective assessment of these symptoms in patients who are aware that their antidepressant has been discontinued. This approach may be affected by biases, which stem from both patients' and clinicians' knowing that treatment has been discontinued. An alternative method is to assess the emergence of adverse events following the discontinuation of double-blind, placebo-controlled antidepressant treatment. This method has the advantage of controlling for clinicians' and patients' biases, as they do not know whether symptoms are related to the active treatment discontinuation. However, both patients and clinicians are aware of the timing of the discontinuation and may be biased to report any symptoms. The most rigorous methodological approach is probably that of blinding patients and clinicians to both the type of treatment and to the timing of the discontinuation.

Another issue is whether to ask open-ended questions in assessing discontinuation reactions (e.g., "Have you experienced any problems or new symptoms during the past week?"). The problem with a general inquiry is that patients may underreport the emergence of psychological and somatic symptoms. Alternatively, a structured interview or a checklist can be used to provide a systematic assessment of possible discontinuation symptoms. The latter approach may potentially bias the patient by suggesting the possibility that specific symptoms may emerge, but it does offer patients the opportunity to review in a careful and systematic fashion all of the possible events that might have happened. A number of initial reports in the literature have relied on spontaneous reports of such events, probably yielding underestimates of the actual occurrence of these events when compared with studies using a systematic inquiry method. However, more recently, almost all the studies of discontinuation reactions have used a systematic inquiry approach to symptom assessment.

Given that the systematic inquiry method is superior to the general inquiry approach, it is not surprising that almost all of the prospective studies in the literature have used the same scale, the Discontinuation-Emergent Signs and Symptoms (DESS) scale.[12] This scale, originally developed by Massachusetts General Hospital investigators to allow for a systematic assessment of discontinuation reactions, was first described by Rosenbaum et al.[12] The DESS (Table 1) is a 43-item scale that can be administered in a clinician-rated form, a self-rated form, or an interactive voice-response form and lists signs and symptoms that have been reported in the available literature of antidepressant discontinuation reactions. Although shorter versions of the 43-item DESS scale are available, the main concern about their use is that the marked heterogeneity of the clinical presentations of discontinuation reactions may lead to the lack of recognition of such events by those versions that do not include all known symptoms associated with antidepressant discontinuation.

EARLY PROSPECTIVE STUDIES OF ANTIDEPRESSANT DISCONTINUATION REACTIONS BASED ON SPONTANEOUS REPORTS

A comparison of the discontinuation reactions between an active treatment and placebo was first reported by Oehrberg et al.[13] This study randomly assigned 120 patients with panic disorder to 12 weeks of treatment with either paroxetine (20–60 mg/day) or placebo, followed by 2 weeks of placebo for both groups of patients. During this 2-week placebo period at the end of the trial, 19 (34.5%) of 55 patients who were treated with paroxetine reported adverse events on discontinuation, as compared with 7 (13.5%) of 52 patients treated with placebo, with dizziness being the adverse event reported with the greatest frequency compared with placebo.

In 1997, our group published a report on the outcome of 20 patients followed at the Depression Clinical and

Table 1. Discontinuation-Emergent Signs and Symptoms (DESS) Scale

Since the last visit, have you experienced any changes in the following symptoms? **(Please check only one response for each symptom)**					
Symptom	(1) New Symptom	(2) Old Symptom, but Worse	(3) Old Symptom, but Improved	(4) Old Symptom, but Unchanged	(5) Symptom Not Present
1. Nervousness or anxiety					
2. Elevated mood, feeling high					
3. Irritability					
4. Sudden worsening of mood					
5. Sudden outbursts of anger ("anger attacks")					
6. Sudden panic or anxiety attacks					
7. Bouts of crying or tearfulness					
8. Agitation					
9. Feeling unreal or detached					
10. Confusion or trouble concentrating					
11. Forgetfulness or problems with memory					
12. Mood swings					
13. Trouble sleeping, insomnia					
14. Increased dreaming or nightmares					
15. Sweating more than usual					
16. Shaking, trembling					
17. Muscle tension or stiffness					
18. Muscle aches or pains					
19. Restless feeling in legs					
20. Muscle cramps, spasms, or twitching					
21. Fatigue, tiredness					
22. Unsteady gait or incoordination					
23. Blurred vision					
24. Sore eyes					
25. Uncontrollable mouth/tongue movements					
26. Problems with speech or speaking clearly					
27. Headache					
28. Increased saliva in mouth					
29. Dizziness, lightheadedness, or sensation of spinning (vertigo)					
30. Nose running					
31. Shortness of breath, gasping for air					
32. Chills					
33. Fever					
34. Vomiting					
35. Nausea					
36. Diarrhea					
37. Stomach cramps					
38. Stomach bloating					
39. Unusual visual sensations (light, colors, geometric shapes, etc.)					
40. Burning, numbness, tingling sensations					
41. Unusual sensitivity to sound					
42. Ringing or noises in the ears					
43. Unusual tastes or smells					

Research Program at Massachusetts General Hospital, as part of a larger, placebo-controlled study of extended-release venlafaxine.[11] At the end of this 8-week, flexible-dose trial of venlafaxine, there was a 1- or 2-week taper of venlafaxine for patients taking 2 or 3 capsules/day (150–225 mg/day), with a dose reduction of 1 capsule/week, and sudden interruption of venlafaxine for patients taking 1 capsule/day (75 mg/day). Our study showed a significantly higher rate of subjects reporting the emergence of adverse events after discontinuation of venlafaxine (78%) compared with those who discontinued placebo (22%). In addition, the mean number of adverse events per subject during the posttaper period was significantly higher in the venlafaxine-treated group (mean: 2.8) compared with the placebo-treated group (mean: 0.4). The most common adverse events after venlafaxine discontinuation were dizziness or light-headedness (N = 4), excessive sweating (N = 2), irritability (N = 2), dysphoria (N = 2), and insomnia (N = 2).[11]

The third prospective study[14] followed patients who were randomly assigned, after 12 to 14 weeks of open-label treatment with fluoxetine, to placebo (N = 96) or to continued fluoxetine (N = 299). Patients were seen at weeks 1, 2, 4, and 6 after randomization. Reports of new or worsened adverse events were similar in both groups for the overall number of patients reporting 1 or more events (placebo: 27%; fluoxetine: 32%; p = .38). However, at week 2, somnolence was significantly more common with placebo (4.4%) than with fluoxetine (0%), and at weeks 4 and 6, dizziness was significantly more common with placebo (6.7% and 5.2%, respectively) than with fluoxetine (1.4% and 0.8%, respectively).[14]

A fourth study examined the spontaneously reported adverse events among patients who had discontinued nefazodone.[15] A total of 165 outpatients with chronic, nonpsychotic major depressive disorder (MDD), MDD plus dysthymic disorder, or recurrent MDD with incomplete interepisode recovery, who achieved and maintained a clinical response during acute and continuation treatment with either nefazodone alone or nefazodone combined with psychotherapy, were randomly assigned to 52 weeks of double-blind nefazodone (maximum dose 600 mg/day) or placebo. Despite an abrupt switch from nefazodone to placebo, there was no evidence of an antidepressant discontinuation syndrome, although the authors compared only the rates of adverse events during the 52-week trial rather than comparing the events that emerged during the first 2 weeks after randomization.[15]

Although these 4 studies probably underestimated the actual rates of discontinuation reactions since they relied on spontaneous reports and did not involve systematic inquiry assessments, they still suggest that a significant proportion of patients will not tolerate abrupt discontinuation of antidepressants such as paroxetine and venlafaxine.

PROSPECTIVE STUDIES OF ANTIDEPRESSANT DISCONTINUATION REACTIONS BASED ON SYSTEMATIC INQUIRY

Our group was first to examine discontinuation reactions with antidepressants prospectively with systematic inquiry.[12] Our study recruited 242 patients whose depression had remitted while receiving maintenance therapy with open-label fluoxetine, sertraline, or paroxetine for 4 to 24 months. Patients then entered a 4-week study period during which they were randomly assigned to a 1-week (from 5 to 8 days), double-blind, placebo substitution period. Systematic assessment of discontinuation reactions was obtained with the 43-item DESS scale, the self-rated Symptom Questionnaire Somatic Symptom subscale,[16] the 28-item, clinician-rated Hamilton Rating Scale for Depression (HAM-D-28),[17] and the clinician-rated Montgomery-Asberg Depression Rating Scale (MADRS).[18]

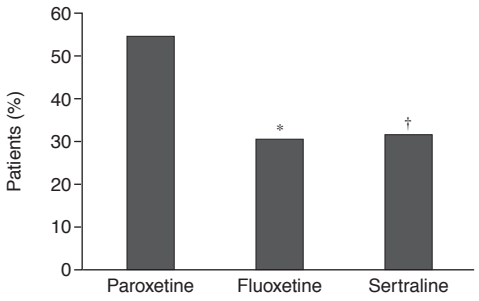
Following treatment interruption, mean increases in the number of DESS events were significant in the sertraline-treated (mean: 5.7) and paroxetine-treated (mean: 7.8) patients but not in the fluoxetine-treated (mean: 0.2) patients. When comparing across groups following treatment interruption, the mean number of DESS events was significantly lower in the fluoxetine-treated patients than in the sertraline-treated or paroxetine-treated patients, and the mean number of DESS events was also significantly lower in the sertraline-treated patients than in the paroxetine-treated patients.

Following treatment interruption, mean changes in Symptom Questionnaire Somatic Symptom subscale, HAM-D-28, and MADRS scores were significant in the sertraline-treated (mean score changes: 2.3, 3.5, and 3.6, respectively) and paroxetine-treated (mean score changes: 3.9, 5.6, and 7.3, respectively) patients, but not in the fluoxetine-treated (mean score changes: –0.2, –0.1, and 0.3, respectively) patients.

When comparing across groups following treatment interruption, the mean Symptom Questionnaire Somatic Symptom subscale scores, the HAM-D-28 scores, and the MADRS scores were significantly lower in the fluoxetine-treated patients than in either the sertraline-treated or paroxetine-treated patients, with no significant differences between sertraline-treated patients and paroxetine-treated patients. When comparing across groups following treatment interruption, the number of events reported spontaneously by 10% or more of the patients was 4 for sertraline (dizziness, 18%; headache, 18%; nervousness, 18%; and nausea, 11%), 8 for paroxetine (dizziness, 29%; nausea, 29%; insomnia, 19%; headache, 17%; abnormal dreams, 16%; nervousness, 16%; asthenia, 11%; and diarrhea, 11%), and 1 for fluoxetine (headache, 16%).

This study had 3 methodological limitations: (1) there was no random assignment to the drug itself, although

Figure 1. Percentage of Paroxetine-, Fluoxetine-, and Sertraline-Treated Patients Who Experienced ≥ 1 Adverse Event During Interruption of Treatment[a]



[a]Reprinted with permission from Fava et al.[19]
*p = .009 vs. paroxetine.
†p = .012 vs. paroxetine.

there was random assignment to placebo substitution; (2) the duration of treatment with each antidepressant was highly variable; and (3) patients and clinicians knew what antidepressant was going to be potentially interrupted, so that the expectations of discontinuation reactions might have been greater among those treated with paroxetine and sertraline. However, the study did support the hypothesis that antidepressants with longer half-lives, such as fluoxetine, have a lower likelihood of discontinuation reactions than antidepressants with a short- (e.g., paroxetine) or intermediate (e.g., sertraline) half-life. The study also clearly showed that spontaneous reports underestimate the occurrence of discontinuation reactions compared with the systematic inquiry approach with the 43-item DESS scale.[12]

As mentioned earlier, while patients in our first, prospective study[12] had not been randomly assigned to SSRI treatment, our subsequent study[19] assessed possible SSRI discontinuation reactions with a randomized, prospective design. During that study, 284 patients with MDD were randomly assigned to double-blind treatment with fluoxetine (N = 67), paroxetine (N = 71), or sertraline (N = 75). The patients who responded following 4 to 10 weeks of short-term treatment entered a 5-month continuation phase, with double-blind 4- to 6-day interruptions of their active treatment. The effects of discontinuation (placebo substitution) were assessed with the 43-item DESS scale. Significantly more patients receiving paroxetine (55%) reported the emergence of 1 or more adverse events following interruption of therapy than did patients treated with fluoxetine (30.4%; p = .009 vs. paroxetine) or sertraline (31.8%; p = .012 vs. paroxetine) (see Figure 1). There was no significant difference between the rates of treatment interruption–related adverse events in patients receiving either fluoxetine or sertraline. The mean number of adverse events was also higher for the patients receiving paroxetine than for those treated with either fluoxetine (p = .01) or sertraline (p = .06).[19]

Our group was also involved in a subsequent study[20] that recruited patients with a history of depression diagnosed by a physician and successfully treated with fluoxetine (20–60 mg), sertraline (50–150 mg), or paroxetine (20–60 mg). At entry, patients had been taking medication continuously for at least 4 months but not more than 3 years, had no dose changes for the 2 months prior to study entry, were taking no other psychoactive medications, and had a score of 10 or less on the 21-item version of the HAM-D (HAM-D-21). Following an initial assessment, the study consisted of two 5-day periods separated by at least 2 weeks but not more than 4 weeks. Under double-blind, order-randomized conditions, all subjects underwent placebo substitution during one 5-day period and continued treatment with their usual SSRI during the next 5-day period. Subjects continued treatment with the SSRI at all other times. Patients completed a 17-item adverse event scale daily for 5 days following study entry and during the 2 blinded periods, with items queried based on the DESS. Each item was rated from 0 to 3 (absent, mild, moderate, or severe), and scores were reported as the change from the most symptomatic of the 5 days immediately following study entry. At baseline and at the end of each 5-day period, the HAM-D-21, the State Anxiety Inventory (SAI), and a self-rated assessment of social and occupational functioning during the previous 4 days were administered. Spontaneous reports of adverse events were also collected at all visits. Thirty-seven of 39 enrolled patients treated with fluoxetine, 34 of 36 treated with sertraline, and 36 of 44 treated with paroxetine completed both blinded periods.[20]

This study showed that placebo substitution, but not continued active medication, was associated with statistically significant increases in total numbers of solicited adverse events for patients treated with paroxetine but not those treated with sertraline or fluoxetine, by the end of the fourth day.[20] Increases in symptoms for patients treated with paroxetine became statistically significant as early as the time of the second dose of placebo.

Mean severity worsened by the end of the fourth day of placebo substitution for 13 of the 17 items on the solicited adverse events scale among patients treated with paroxetine, for 3 of 17 among patients treated with sertraline, and for no items among patients treated with fluoxetine. Among patients taking paroxetine, mean severity of most items increased by between 0.5 and 1 on the 4-point scale. For both paroxetine-treated and sertraline-treated patients, dizziness was the item with the greatest number of patients reporting an increase in severity. Patients taking paroxetine also experienced statistically significantly worsened severity in nausea, unusual dreams, tiredness or fatigue, irritability, unstable or rapidly changing mood, difficulty concentrating, muscle aches, feeling tense, chills, trouble sleeping, agitation, and diarrhea during placebo substitution relative to active treatment. Patients treated with ser-

traline experienced statistically significantly worsened severity in dizziness, nausea, and unusual dreams during placebo substitution relative to active treatment.

Spontaneously reported adverse events followed a pattern similar to that of solicited events, with increases for patients treated with paroxetine in dizziness (placebo substitution 33.3%, active treatment 0.0%; $p < .001$), headache (placebo substitution 27.8%, active treatment 5.5%; $p = .008$), nausea (placebo substitution 16.7%, active treatment 0.0%; $p = .031$), and anxiety (placebo substitution 16.7%, active treatment 2.8%; $p = .025$).[20] Among patients treated with sertraline, there was an increase in the number spontaneously reporting dizziness during placebo interruption (placebo substitution 35.3%, active treatment 5.9%; $p = .007$). Among patients treated with fluoxetine, there was no statistically significant increase in spontaneous reports of any symptom during placebo substitution.

At the end of the placebo substitution period, patients taking paroxetine, but not those taking fluoxetine or sertraline, demonstrated statistically significant increases in HAM-D-21 and SAI scores compared with patients who continued taking the active drug. Patients treated with paroxetine reported statistically significant deterioration in functioning at work, relationships, social activities, and overall functioning, while patients treated with sertraline reported deterioration in overall functioning, and patients treated with fluoxetine reported no change in any area of functioning following placebo substitution.[20] Mean ± SD plasma drug concentrations (ng/mL) during active treatment and following placebo substitution, respectively, were as follows: fluoxetine/norfluoxetine: active 264.6 ± 160.3, placebo substitution 197.7 ± 132.5, mean percentage reduction 29.7% ± 15.8%; sertraline/desmethylsertraline: active 87.7 ± 63.0, placebo substitution 26.0 ± 33.0, mean percentage reduction 73.5% ± 11.7%; paroxetine: active 46.7 ± 33.4, placebo substitution 6.9 ± 11.8, mean percentage reduction 86.7% ± 12.9%. Percentage reduction in plasma concentrations across drug groups was statistically significantly correlated with new adverse events ($r = 0.56$, $p < .01$); however, within individual drug groups, correlations between new events and percentage reduction in concentration were not significant (fluoxetine $r = 0.0$, $p = .98$; sertraline $r = 0.19$, $p = .30$; paroxetine $r = 0.27$, $p = .13$). Neither absolute drug concentration in the steady state nor absolute change in concentration after interruption correlated with emergence of new symptoms following treatment interruption for any group.[20] This study supported the observation of our previous study[19] that paroxetine treatment is significantly more likely to be associated with discontinuation reactions than both sertraline and fluoxetine and that no major differences are notable during relatively short treatment interruptions between fluoxetine and sertraline.

Data from a previously completed placebo-controlled, double-blind study designed to assess citalopram in depression relapse prevention were analyzed[21] to assess patients for the emergence of discontinuation effects following random assignment to placebo after 8 weeks of active drug treatment. Side effects that occurred during the first 2 weeks following random assignment to active drug ($N = 150$) or placebo ($N = 72$) were measured using the Udvalg for Kliniske Undersogelser (UKU) unwanted side effect scale. The proportion of patients who experienced 1 or more events over the 2-week period following randomization was similar in the 2 groups, and there was no association between citalopram dose prior to random assignment and the reporting of symptoms.[21] The exposure to citalopram treatment in this study was relatively short (8 weeks) and may account for the relative lack of findings. In addition, the UKU scale was not developed specifically to assess discontinuation reactions but primarily to evaluate side effects from psychotropic medications and may therefore be less sensitive than the DESS scale in these types of studies.

A study by Hindmarch and colleagues[22] examined the effects of discontinuing and resuming antidepressant treatment with 4 SSRIs on cognitive and psychomotor function. Eighty-seven patients receiving maintenance therapy with fluoxetine, sertraline, paroxetine, or citalopram had their treatment interrupted for 4 to 7 days using a double-blind, placebo substitution design. Assessments of aspects of cognitive and psychomotor performance, mood, and symptoms were carried out at each visit. Following interruption of treatment, paroxetine-treated patients experienced significantly more cognitive failures ($p = .007$), poorer quality of sleep ($p = .016$), and an increase in depressive symptoms, as rated both subjectively, using the Zung scale ($p = .006$), and by the clinician, using the MADRS ($p = .0003$) and the Clinical Global Impressions scale ($p = .0003$), compared with some or all of the other drugs. All changes were reversed on reinstatement of treatment.[22]

A more recent study[23] examined the effects of relatively short antidepressant treatment interruptions (3–5 days). Patients successfully treated for depression with fluoxetine or paroxetine underwent treatment interruption in a double-blind fashion. Treatment interruption–emergent symptoms were assessed using the DESS checklist. Other assessments included the MADRS, the Clinical Global Impressions-Severity of Illness scale, and a social functioning questionnaire. Of 150 patients enrolled, 141 completed the study. Following treatment interruption, fluoxetine-treated patients experienced fewer treatment interruption–emergent events than did paroxetine-treated patients. The paroxetine treatment group also experienced significant increases in depressive symptoms, Clinical Global Impressions-Severity of Illness scores, and difficulty in social functioning; the fluoxetine treatment group did not.[23]

Another study[24] investigated the incidence and characteristics of the discontinuation syndrome in patients who stopped treatment with the SSRIs paroxetine and fluoxe-

tine under the usual conditions of clinical practice. Ninety-seven outpatients who received an initial diagnosis of dysthymic disorder, who responded to ≥ 8 weeks of treatment with paroxetine (N = 52) or fluoxetine (N = 45), and who discontinued the SSRI according to their psychiatrist's instructions, were included. They were assessed at the time of discontinuation using a semistructured interview for clinical and treatment characteristics, the HAM-D, and the MADRS. Patients were then assessed 4 weeks later using a checklist for discontinuation symptoms, a semistructured interview for discontinuation symptom characteristics, the HAM-D, and the MADRS. A discontinuation syndrome was found in 26 patients (26.8% of our sample); of this group, 22 patients (84.6%) had received paroxetine, and 4 patients (15.4%) had received fluoxetine. The mean time to onset of symptoms was 2 days after drug discontinuation, and the mean duration of symptoms was 5 days.[24]

A small study examining the brain magnetic resonance spectroscopy correlates of antidepressant discontinuation reactions found that 4 (31%) of 13 patients treated with paroxetine and 2 (15%) of 13 patients treated with fluoxetine met criteria for a discontinuation syndrome, using a modified, 23-item DESS scale.[25] A limitation of this study was the fact that the use of a shorter version of the DESS may have reduced the sensitivity of the instrument to differences across antidepressants in rates of discontinuation reactions.

A recent study assessed the relative risk of emergence of adverse events on venlafaxine versus escitalopram discontinuation with the 43-item version of the DESS scale.[26] Following an 8-week, randomized, double-blind study comparing the efficacy and tolerability of escitalopram (10–20 mg/day; N = 148) to that of venlafaxine extended release (75–150 mg/day; N = 145) in primary care patients with MDD, at the end of the 1-week run-out period (week 9), a total of 23 symptoms were reported on the DESS, with an incidence ≥ 10% in either treatment group: 5 symptoms in the escitalopram group and 23 symptoms in the venlafaxine group. Of these, a total of 11 symptoms occurred with a statistically significantly higher incidence in the venlafaxine group than in the escitalopram group. While at week 8, the mean number of DESS symptoms was similar in the 2 treatment groups (1.2 in the escitalopram group vs. 1.5 in the venlafaxine group), at week 9, the mean number of DESS symptoms in the venlafaxine group (mean: 5.0) was significantly ($p < .001$) higher than that in the escitalopram group (mean: 2.4). Significantly more venlafaxine-treated patients than escitalopram-treated patients had a change in DESS score ≥ 4 from week 8 to week 9 ($p < .01$, Fisher exact test).[26] The findings of the study suggest that treatment with escitalopram, with an intermediate half-life, is significantly less likely to be associated with the emergence of discontinuation symptoms than the short-acting venlafaxine in its extended release formulation, which confirms a prior report from our group.[11]

The effects of an abrupt interruption of agomelatine, a new melatonergic/serotonergic antidepressant, were explored in a double-blind, placebo-controlled study.[27] Paroxetine was used as an active control. After 12 weeks of double-blind treatment with agomelatine 25 mg/day or paroxetine 20 mg/day, sustained remitted depressed patients were randomly assigned for 2 weeks under double-blind conditions to placebo or to their initial antidepressant treatment. Discontinuation symptoms were assessed at the end of the first and second week of discontinuation with the 43-item DESS checklist. One hundred ninety-two sustained remitted patients were randomly assigned to the 2-week discontinuation period. Patients who discontinued agomelatine did not experience more discontinuation symptoms than those who continued on agomelatine therapy. Patients who discontinued paroxetine for placebo experienced significantly more DESS discontinuation symptoms, during the first week, compared with those who continued with paroxetine (respective mean number of emergent symptoms: 7.3 ± 7.1 and 3.5 ± 4.1, $p < .001$). Eight emergent discontinuation symptoms were reported significantly more frequently by patients who interrupted paroxetine compared with those continuing on paroxetine therapy. No significant difference was shown between the continuing and interrupting groups in the second week of discontinuation. In contrast to paroxetine, abrupt cessation of agomelatine was not observed to be associated with discontinuation symptoms.[27] This study clearly confirms the results of previous studies from our group suggesting that paroxetine is associated with an increased risk of discontinuation reactions and that the putative antidepressant agomelatine may be associated with minimal or no discontinuation reactions.

CONCLUSION

The prospective assessment of discontinuation-emergent symptoms is very important to our field. Discontinuation reactions have been reported with all antidepressant classes, and they may be associated with significant somatic and psychological distress. Although clinicians have traditionally used spontaneous reports to estimate the relative risk for discontinuation reactions, it is clear from a number of prospective studies that spontaneous reports are likely to underestimate the occurrence of discontinuation reactions and that systematic inquiry needs to be part of the assessment in antidepressant discontinuation studies. Instruments such as the 43-item DESS scale may provide our field with some insight into the number and type of events that may occur following antidepressant discontinuation. Discontinuation reactions may vary in frequency across antidepressants. Separate studies using prospective, systematic inquiry assessments have shown that

antidepressants with relatively shorter half-lives (e.g., paroxetine and venlafaxine) are more likely to have discontinuation reactions than antidepressants with longer half-lives (e.g., fluoxetine, sertraline, and escitalopram). One limitation is that all these studies, except one in panic disorder, were done in MDD, and we therefore do not know if these findings are generalizable to non-MDD patients. Future studies should attempt to characterize predictors of discontinuation reactions from a neurobiological and pharmacogenetic standpoint.

Drug names: citalopram (Celexa and others), clomipramine (Anafranil and others), escitalopram (Lexapro), fluoxetine (Prozac and others), paroxetine (Paxil, Pexeva, and others), phenelzine (Nardil), sertraline (Zoloft), venlafaxine (Effexor).

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