CME ACTIVITY

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CME Objectives

After completing this CME activity, the psychiatrist should be able to:

- Recognize the development of manic symptoms from antidepressant discontinuation in bipolar patients
- Determine whether conventionally accepted antidepressants have mood-stabilizing properties based on the overlap between symptoms of mania and psychiatric antidepressant withdrawal symptoms
- Distinguish the characteristics of antidepressant discontinuation–related mania from antidepressant induction, agitated depression, physiologic withdrawal, and course of illness

Statement of Need and Purpose

Physicians responding to articles in *The Journal of Clinical Psychiatry* and its related CME activities have indicated a need to know more about the management of antidepressant discontinuation–related mania as it relates to bipolar disorder. This CME enduring material presents current information to address that need. There are no prerequisites for participating in this CME activity.

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Antidepressant Discontinuation–Related Mania: Critical Prospective Observation and Theoretical Implications in Bipolar Disorder

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Background: Development of manic symptoms on antidepressant discontinuation has primarily been reported in unipolar patients. This case series presents preliminary evidence for a similar phenomenon in bipolar patients.

Method: Prospectively obtained life chart ratings of 73 bipolar patients at the National Institute of Mental Health were reviewed for manic episodes that emerged during antidepressant taper or discontinuation. Medical records were utilized as a corroborative resource. Six cases of antidepressant discontinuation–related mania were identified and critically evaluated.

Results: All patients were taking conventional mood stabilizers. The patients were on antidepressant treatment a mean of 6.5 months prior to taper, which lasted an average of 20 days (range, 1–43 days). First manic symptoms emerged, on average, 2 weeks into the taper (range, 1–23 days). These 6 cases of antidepressant discontinuation–related mania involved 3 selective serotonin reuptake inhibitors (SSRIs), 2 tricyclic antidepressants (TCAs), and 1 serotonin-norepinephrine reuptake inhibitor. Mean length of the ensuing manic episode was 27.8 days (range, 12–49 days). Potential confounds such as antidepressant induction, phenomenological misdiagnosis of agitated depression, physiologic drug withdrawal syndrome, and course of illness were carefully evaluated and determined to be noncontributory.

Conclusion: These 6 cases suggest a paradoxical effect whereby antidepressant discontinuation actually induces mania in spite of adequate concomitant mood-stabilizing treatment. These preliminary observations, if replicated in larger and controlled prospective studies, suggest the need for further consideration of the potential biochemical mechanisms involved so that new preventive treatment approaches can be assessed.

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Standard clinical practice for treatment of bipolar depression invariably includes the addition of an antidepressant to a mood-stabilization regimen.[1] Of concern, however, is the induction of mania; retrospective reviews have estimated the rate of mania to be as high as 35% for all antidepressant classes.[2] Although not guided by controlled literature, clinicians usually taper and discontinue antidepressant agents if an adequate trial has not proved clinically efficacious or once some degree of euthymia has been maintained.

Discontinuation of a psychotropic medication resulting in mood relapse or physiologic drug withdrawal symptoms is common. Relapse upon discontinuation of maintenance antidepressant treatment in unipolar patients is well described,[3] as is manic relapse upon discontinuation of maintenance mood-stabilizing agents such as lithium and carbamazepine in bipolar patients.[4,5]

An entire cluster of withdrawal symptoms (including gastrointestinal distress, movement disorders, insomnia, anxiety, and mood fluctuations) have been associated with discontinuation of tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs).[6–8] Additionally, Zajecka and colleagues[9] have recently proposed an operationalized definition for the physical and psychological symptoms reported upon discontinuation of selective serotonin reuptake inhibitors (SSRIs), also known as the "serotonin reuptake inhibitor discontinuation syndrome"; hallmark to this definition are both somatic and psychic

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symptoms including dizziness, light-headedness, insomnia, fatigue, nausea, headache, sensory disturbance, and anxiety/agitation. The only controlled study to date on antidepressant discontinuation[10] showed differential rates of withdrawal symptoms on discontinuation of various SSRIs. Presumably owing to a longer metabolic half-life, discontinuation of fluoxetine was associated with fewer withdrawal symptoms than either sertraline or paroxetine.

The overlap between symptoms of mania and psychiatric antidepressant withdrawal symptoms led us to question whether conventionally accepted antidepressants have mood-stabilizing (i.e., antimanic) properties. In what would now be considered an extraordinary study, Akimoto[11] found 12 (86%) of 14 and 3 (100%) of 3 manic patients had a marked improvement or complete remission with imipramine and amitriptyline monotherapy, respectively. This observation prompted only one controlled study by Klein,[12] in which imipramine was found to be no better than placebo for the treatment of mania.

Over a decade later, numerous case reports of antidepressant discontinuation–induced mania or hypomania have been reported in the literature.[13–22] The majority (81%) of reported cases chronicle the development of such symptoms in a unipolar (no history of mania) depressed patient population following TCA discontinuation. Far less frequently described, however, and seemingly more confounded, is mania associated with antidepressant discontinuation in bipolar patients. In a retrospective study, Shriver and colleagues[23] report that 12 (15%) of 79 episodes of mania in 39 patients occurred within 2 weeks of antidepressant discontinuation. Of the 12 episodes of mood elevation corresponding with antidepressant discontinuation, 7 (58.3%) were associated with SSRI treatment, 3 (25%) with MAOI treatment, 1 (8.3%) with serotonin-norepinephrine reuptake inhibitor (SNRI) treatment, and 1 (8.3%) with TCA treatment.

To add to the literature and promote further discussion and study of this phenomenon, we present 6 cases of apparent antidepressant discontinuation–related mania in bipolar patients. This cohort was selected from a prospective data set and may be critically distinguished from mania induction by antidepressant treatment, phenomenological misdiagnosis of agitated depression, physiologic antidepressant withdrawal syndrome, and natural course of illness variables.

METHOD

The study cohort included 73 patients participating in clinical trials at the Biological Psychiatry Branch, National Institute of Mental Health (NIMH). The bipolar diagnosis of each patient was confirmed by the Schedule for Affective Disorders and Schizophrenia[24] or the Structured Clinical Interview for DSM-IV.[25] Mood, functioning, and medications were prospectively tracked daily in a blinded fashion (in the majority of cases) by both patient and clinician using the NIMH life chart methodology (LCM),[26] which has been shown to be a reliable and valid instrument for prospective mood tracking.[27] Each patient's retrospective LCM documents previous course of illness with particular emphasis on past episodes, illness pattern, hospitalizations, and treatments.

We primarily identified episodes of mania from the prospective LCM data that emerged during antidepressant taper or within 1 week of antidepressant discontinuation. The manic episodes reported by both clinician and patient on the prospective LCM were then secondarily corroborated by medical record review. Our clinical team next critically evaluated the prospective LCM data in a nonblind fashion to exclude cases in which mood elevation may be alternately attributed to (1) antidepressant induction (the antidepressant appeared to induce the mania and therefore was quickly withdrawn), (2) phenomenological misdiagnosis of agitated depression as dysphoric mania, (3) physiologic antidepressant withdrawal syndrome, or (4) course of illness (i.e., seasonality) and therefore likely not related to antidepressant discontinuation.

RESULTS

As presented in Table 1, all 6 patients were taking lithium for mood stabilization (mean lithium level = 0.95 mmol/L; range, 0.5–1.1 mmol/L). Patients were on antidepressant treatment for a mean of 6.5 months (203 days; range, 35–480 days) prior to the taper. The antidepressant treatment was discontinued owing to nonresponse in 4 cases and euthymia in 2 cases. The mean length of antidepressant taper was 19.7 days (range, 1–43 days), while the mean onset of manic symptoms occurred 13.5 days (range, 1–23 days) into the taper. In one case (patient 6) the antidepressant treatment was abruptly discontinued owing to a drug fever.

Of these 6 episodes of antidepressant discontinuation–related mood elevation, 3 were associated with an SSRI (2 sertraline, 1 fluoxetine), 1 with an SNRI (venlafaxine), and 2 with a TCA (1 desipramine, 1 nortriptyline). Five of the cases were classified as "moderate mania" by clinician ratings on the functional impairment scale of the LCM during the worst period of the episode, and 1 case was a hypomanic episode. Two patients exhibited classic

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Table 1. Demographics of Antidepressant Discontinuation–Related Mania

Patient	Mood Stabilization Treatment	Blood Lithium Level (mmol/L)	Antidepressant Daily Dose (mg)	Time Taking Antidepressant Before Taper (days)	Antidepressant Taper (days)	First Symptoms (days from start of taper)	Episode Type	Mania Length (days)	Antimanic Treatment (daily dose)
1	Lithium Carbamazepine	1.1	Sertraline, 200	90	11	11	Euphoric→ dysphoric; hospitalized	49	Perphenazine, 4 mg
2	Lithium Carbamazepine	1.0	Fluoxetine, 70	140	43	23	Euphoric→ dysphoric	49	Thioridazine, 175 mg
3	Lithium	1.0	Desipramine, 450	330	20	20	Euphoric	21	Perphenazine, 32 mg
4	Lithium Valproic acid	0.5	Venlafaxine, 150	480	29	13	Dysphoric	22	Antidepressant reinstitution, 100 mg
5	Lithium	1.1	Nortriptyline, 50	143	14	13	Dysphoric hypomania	14	None
6	Lithium	1.0	Sertraline, 150	35	1[a]	1	Dysphoric	12	Thioridazine, 200 mg
Means				203	19.7	13.5		27.8	

[a]Abrupt discontinuation due to drug fever.

Table 2. Potential Mania-Related Confounds

Patient	Induction by Antidepressant[a] (total exposure)	Agitated Depression?	Physiologic Withdrawal Syndrome[b]	Related to Course of Illness?
1	No (12 weeks)	Yes: irritable No: grandiose, impulsive, racing thoughts	No	No: mood stability for 8 months; medications unchanged prior to taper
2	No (17 weeks)	Yes: decreased sleep No: euphoric, compulsive cleaning, pressured speech	No	No: mood stability for 14 months; medications unchanged prior to taper; unequaled severity prior/since
3	No (44 weeks)	Yes: cognitive disorganization, decreased sleep No: increased energy, impulsive	No	No: seasonal manias in October and May; this episode in February
4	No (20 weeks)	Yes: irritable No: grandiose	Yes: headache, fatigue	Yes: manic symptoms precede taper No: increased density and duration; medications unchanged prior to taper
5	No (17 weeks)	Yes: distractible No: grandiose	No	No: mood stability for 4 months; medications unchanged prior to taper
6	Yes (4.5 weeks)	No: grandiose, impulsive, pressured speech, racing thoughts	No	No: unequaled severity and duration prior/since

[a]Antidepressant-induced mania typically develops 3–6 weeks after antidepressant institution (Wehr and Goodwin[28]).
[b]As operationally defined by Zajecka et al.[9]

progression from euphoric to dysphoric mania. The mean length of the manic episode was 27.8 days (range, 12–49 days). One patient was hospitalized for a period of 19 days owing to manic symptoms while the others were managed on an outpatient basis. Characteristics of each patient's antidepressant discontinuation–related mania that distinguish it from antidepressant induction, agitated depression, physiologic withdrawal, and course of illness are presented in Table 2.

DISCUSSION

This case series presents data consistent with an antidepressant discontinuation–related mania phenomenon. The very nature of bipolar disorder makes it difficult to attribute causality of mood episodes with certainty. We therefore considered 4 possible confounds to antidepressant discontinuation–related mania.

The literature describes antidepressant-induced mania[28] and antidepressant-induced cycle acceleration[2] as typically occurring in the same 4- to 8-week time period associated with antidepressant response. By this criterion, causality by antidepressant induction seems very unlikely in all but one case (patient 6, 4.5 weeks exposure), since the mean drug exposure time was 6 months prior to antidepressant discontinuation. Furthermore, in 3 of the 6 patients (2, 4, and 6), the mania in question was more severe and dense than that patient's other manic episodes (both by prospective and retrospective LCM review), which stands in contrast to findings by Stoll et al.[29] in which an-

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tidepressant-induced mania was found to be milder and briefer than spontaneous mania. Finally, Wehr and Goodwin[30] reported that in suspected cases of cycling induction, discontinuation of antidepressants may be associated with periods of remission. Not only are these 6 cases noncycling, but none of the cases described here experienced remission thereafter. Thus, the phenomenon of antidepressant discontinuation–related mania appears to be distinguished from antidepressant-induced mania and cycle acceleration. Of additional interest, and perhaps suggestive of a mood-stabilizing effect of antidepressants, is the partial mania resolution after reinstitution of the antidepressant agent (venlafaxine) in patient 4.

Upon retrospective LCM review, 5 of the 6 patients have no history of antidepressant-induced mania or cycle acceleration. Patient 5 experienced one previous nortriptyline-induced manic episode within 2 weeks of drug initiation. On further follow-up, 2 patients have since experienced 2 episodes each of mood elevation that appear to be associated with antidepressant discontinuation.

Phenomenologically, agitated depression can be difficult to distinguish from dysphoric mania. Although not conclusive, we were able to differentiate the 2 states when the dysphoria was preceded by euphoria (1 and 2) or when core manic symptoms were clearly identified (patients 3, 4, 5, and 6).

Again, there can be overlap between the psychiatric symptoms of a physiologic withdrawal syndrome and mania. Seventy-two percent (31/43) of the symptoms on the Discontinuation-Emergent Signs and Symptoms checklist[10] are primarily somatic, yet 5 of the cases presented here experienced prominent mood symptoms with little to no report of bothersome physical symptoms. Additionally, if this were a strictly physiologic withdrawal phenomenon, symptom abatement would be expected on drug elimination, yet the length of ensuing manic episode (mean = 21 days) does not support this explanation. Clearly, this period allows adequate time for metabolic clearance of the primary and parental compound, thus rendering the phenomenon we describe unlikely attributable to physiologic withdrawal alone.

The most challenging differential to antidepressant discontinuation–related mania in bipolar patients is mania occurring as part of the patient's expected course of illness. The retrospective assessment of prospective LCM data do allow, however, critical assessment of seasonal liability, manic severity, and previous postdepression manic episodes. Of the 6 cases of antidepressant discontinuation–related mania presented, each appears distinct in terms of seasonal liability, severity, and prior pattern of illness.

This case series is limited by the small number of cases presented, the absence of a control group, and the lack of large retrospective or prospective literature to guide in our assessment. Additionally, while the data for this study were collected prospectively without intent of identifying the present phenomenon, its retrospective interpretation is not immune to bias. The authors have attempted to minimize any bias by considering other possible perspectives (see Table 2).

The study of this phenomenon may be further complicated by the lack of a true animal model for mania, whereby the effect of antidepressant treatments could subsequently be evaluated. The low reported incidence of this phenomenon may be accounted for by episode misattribution and/or the current trend toward use of multiple mood-stabilizing agents, thus serving as prophylaxis against discontinuation-related mania in the midst of antidepressant taper.

While the precipitation of a manic episode from the discontinuation of an antidepressant agent appears paradoxical, some preliminary speculation has been put forth in the literature attempting to explain the biological mechanism whereby this phenomenon may occur. For example, Dilsaver and colleagues[15,31] have proposed that withdrawal-induced cholinergic overdrive can mobilize monoaminergic systems, resulting in manic symptomatology. Zajecka et al.[9] proposed that the presynaptic reuptake blockade of serotonin by antidepressants over time results in desensitization of postsynaptic serotonin and norepinephrine receptors. Antidepressant discontinuation after chronic treatment may result in acute enhancement of reuptake, thus depleting serotonin and resulting in a hyposerotonergic state of mania. Noradrenergic and dopaminergic receptor sensitization may also occur and in similar fashion may explain why TCA as well as MAOI discontinuation-related manias have been reported.[23,31]

Clinical experience shows that many psychotropic medications are successfully utilized as treatments outside of our conventionally accepted definition, including the tricyclically configured anticonvulsant carbamazepine for mood stabilization[32,33]; the anticonvulsant valproic acid for panic disorder[34]; nefazodone, an SNRI, for treatment of dysphoric mania[35]; the typical neuroleptics haloperidol and thiothixene for bipolar depression[36]; the TCAs trimipramine[37] and amoxapine[38] for primary psychotic disorders; and clozapine, an atypical neuroleptic, for mood stabilization.[39] Along these lines, perhaps reconceptualizing antidepressants as mood stabilizers for some bipolar patients may be warranted based on the premise that treatment for mood episodes may be less about directionality

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of mood (mania vs. depression) than amplitude of change from euthymia and normal brain function.

Given the case reports, further research into antidepressant discontinuation–related mania is encouraged, including its mechanism of action, prevalence, drug-related differences, and implications in the treatment of bipolar disorder.

Drug names: amitriptyline (Elavil and others), amoxapine (Asendin and others), carbamazepine (Tegretol and others), clozapine (Clozaril), desipramine (Norpramin and others), fluoxetine (Prozac), haloperidol (Haldol and others), nefazodone (Serzone), nortriptyline (Pamelor and others), paroxetine (Paxil), perphenazine (Trilafon and others), sertraline (Zoloft), thioridazine (Mellaril and others), thiothixene (Navane), trimipramine (Surmontil), valproic acid (Depakene), venlafaxine (Effexor).

Disclosure of off-label usage: The authors of this article have determined that, to the best of their knowledge, no investigational information about pharmaceutical agents has been presented herein that is outside Food and Drug Administration–approved labeling.

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Instructions

Psychiatrists may receive 1 hour of Category 1 credit toward the American Medical Association Physician's Recognition Award by reading the article starting on page 563 and correctly answering at least 70% of the questions in the posttest that follows.

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1. Which of the following is *not* a hallmark symptom in the physiologic withdrawal syndrome referred to as the "serotonin reuptake inhibitor discontinuation syndrome"?

a. Dizziness
b. Anxiety
c. Nausea
d. Tinnitus

2. Antidepressant-induced mania typically occurs:

a. Within 3–5 days of drug initiation
b. In the same 4- to 8-week period associated with drug response
c. At any given time on the drug
d. 6 months into drug treatment

3. According to the cases presented, antidepressant discontinuation–related mania appears to be:

a. Less severe than spontaneous mania
b. No different from spontaneous mania
c. More severe than spontaneous mania
d. No different from antidepressant-induced mania

4. An argument against this phenomenon being purely physiologic includes:

a. The 6 cases presented all had mood symptoms in addition to their prominent somatic symptoms
b. Only 4 of the 6 experienced dizziness and nausea
c. None of the 6 experienced any physiologic disturbance
d. Mood symptoms did not clear when the antidepressant was eliminated from the system

5. Which of the following is a possible explanation for the low reported incidence of antidepressant discontinuation–related mania?

a. The common use of mood stabilizers in combination with antidepressants
b. Minimal use of antidepressants with bipolar patients
c. The practice of gradual antidepressant discontinuation
d. Abrupt antidepressant discontinuation

6. In the study, mood elevations were attributed to induction by antidepressant discontinuation only when which of the following was ruled out?

a. Previous history of antidepressant-induced mania
b. Previous history of antidepressant use
c. Antidepressant induction, misdiagnosis, physiologic syndrome, and course of illness
d. History of antidepressant-discontinuation induction, physiologic syndrome, and seasonal pattern to mania

7. What theoretical explanation do the authors offer for the observed phenomenon?

a. Treatment recommendations may be based on change from normal brain function
b. Treatment recommendations may be based on polarity of mood
c. Physiologic withdrawal syndrome was mistaken for mania
d. The manic episodes described were simply course of illness

Answers to the February 1999 CME posttest

1. d 2. c 3. e 4. b 5. a 6. b 7. e

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Circle the one correct answer for each question.

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3.	a	b	c	d
4.	a	b	c	d
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Please evaluate the effectiveness of this CME activity by answering the following questions.

1. Was the educational content relevant to the stated educational objectives? ❑ Yes ❑ No
2. Did this activity provide information that is useful in your clinical practice? ❑ Yes ❑ No
3. Was the format of this activity appropriate for the content being presented? ❑ Yes ❑ No
4. Did the method of presentation hold your interest and make the material easy to understand? ❑ Yes ❑ No
5. Achievement of educational objectives:
   A. Enabled me to recognize the development of manic symptoms from antidepressant discontinuation in bipolar patients. ❑ Yes ❑ No
   B. Enabled me to determine whether conventionally accepted antidepressants have mood-stabilizing properties based on the overlap between symptoms of mania and psychiatric antidepressant withdrawal symptoms. ❑ Yes ❑ No
   C. Enabled me to distinguish the characteristics of antidepressant discontinuation–related mania from antidepressant induction, agitated depression, physiologic withdrawal, and course of illness. ❑ Yes ❑ No
6. Did this CME activity provide a balanced, scientifically rigorous presentation of therapeutic options related to the topic, without commercial bias? ❑ Yes ❑ No
7. Does the information you received from this CME activity confirm the way you presently manage your patients? ❑ Yes ❑ No
8. Does the information you received from this CME activity change the way you will manage your patients in the future? ❑ Yes ❑ No
9. Please offer comments and/or suggested topics for future CME activities.

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