Antidepressant-Withdrawal Mania: A Critical Review and Synthesis of the Literature

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Background: Hypomania or mania have rarely been reported to develop shortly after the discontinuation of an antidepressant drug. The true incidence of this discontinuation syndrome is unknown because it may be underreported as a consequence of underrecognition or misattribution. This article examines the possible etiology, nosology, mechanisms, and other aspects of the syndrome.

Data Sources and Study Selection: A PubMed search was conducted in May 2003 and repeated in January 2004 using the search terms antidepressant and mania. Relevant articles containing adequate descriptions for presentation were retrieved, and their reference lists were handsearched for further pertinent material. Handsearches of the indexes of leading psychiatry journals were also performed for the years 1998– 2003. Twenty-three articles were identified for review.

Conclusions: Antidepressant-withdrawal hypomania or mania may occur rarely with almost any antidepressant drug after sudden withdrawal, tapered discontinuation, or even merely a decrease in dose. The syndrome may be selflimiting, may abate with the reinstitution of the antidepressant drug, or may require specific antimanic treatments; mood stabilizers do not necessarily protect against the syndrome. The true incidence of the syndrome is unknown. Narrow and broad diagnostic criteria are proposed for the syndrome, and a synthesis of literature is provided. (*J Clin Psychiatry 2004;65:987–993*)

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Corresponding author and reprints: Chittaranjan Andrade, M.D., Department of Psychopharmacology, National Institute of Mental Health and Neurosciences, Bangalore, 560 029, India (e-mail: andrade@nimhans.kar.nic.in). t is well known that depressed patients sometimes switch into hypomania or mania after the institution of antidepressant drug therapy.¹ It is also well known that the sudden discontinuation of an antidepressant drug may elicit an unpleasant withdrawal reaction.²⁻⁴ It is, however, less well known that the sudden withdrawal of an antidepressant drug may rarely precipitate hypomania or mania. The literature on the subject consists almost exclusively of case reports and a few small open studies; this article briefly reviews that literature. Subsequently, an attempt is made to better define the syndrome and to understand its etiology, nosology, frequency of occurrence, treatment, and other related issues.

In the review and accompanying discussion, hypomania will be distinguished from mania to the extent that the original authors made the distinction; otherwise, the more generic term *antidepressant-withdrawal mania* will be applied.

METHOD

A PubMed search was conducted in May 2003 and repeated in January 2004 using the search terms *antidepressant* and *mania*. Relevant articles containing adequate descriptions for presentation were retrieved, and their reference lists were hand-searched for further pertinent material. Hand-searches of the indexes of leading psychiatry journals were also performed for the years 1998–2003.

RESULTS

Twenty-three articles were identified for review. These articles are reviewed approximately in chronological order of year of publication. Very few articles provided information that would help the reader apply the narrow versus broad criteria for antidepressant-withdrawal mania as suggested in Table 1. Therefore, only a dichotomous decision was possible in most instances as to whether the cases described in the articles were likely or unlikely to be antidepressant-withdrawal mania as conceptualized in this review. Articles that provided more useful information are discussed in greater detail.

The first report of antidepressant-withdrawal mania in the literature was probably that of Mirin et al.⁵ These

authors described 1 bipolar patient and 6 unipolar patients who developed hypomania (N = 5) or mania (N = 2) 2–7 days after the withdrawal of a tricyclic antidepressant (TCA) drug. The agents withdrawn were amitriptyline (N = 5), imipramine (N = 1), and protriptyline (N = 1). Three patients had withdrawn their medication abruptly, and 4 had tapered their drugs over 2–8 weeks. Three patients responded promptly (5–9 days) to neuroleptic drugs; the remaining 4, 1 of whom was taking lithium and 3 of whom were drug-free, experienced more gradual (2– 4 weeks) resolution of symptoms. In at least 2 patients,

into depression. In a small systematic study of the effects of sudden antidepressant drug discontinuation, Charney et al.⁶ found that withdrawal hypomania developed in 1 of 7 depressed patients. The symptoms began within a week of the abrupt discontinuation of amitriptyline and abated spontaneously within the second week. Withdrawal hypomania was also described in 2 depressed men after desipramine was suddenly (N = 1) or gradually (N = 1) stopped⁷; in both patients, the hypomania developed within 2 days of the withdrawal of the drug and remitted when the drug was reinstituted. One patient had a family history of bipolar illness, and the other patient had bipolar II disorder.

resolution of the hypomania was followed by a relapse

In a review, Dilsaver and Greden² listed 2 of their cases, both of which involved women with unipolar depression. Both women developed hypomania 2–3 days after the withdrawal of imipramine. The syndrome was self-limiting; relapse into depression occurred following 3 days in 1 woman and following 3 weeks in the other.

Although trazodone-withdrawal hypomania was reported in a depressed woman,⁸ the syndrome is unlikely to have been drug-related because it occurred as late as 3 weeks following a tapered discontinuation spanning 2 months. Withdrawal mania, reported in a man who had remained euthymic taking imipramine for 12 years,⁹ is also very likely to have been a spontaneous manic episode because the drug withdrawal was effected over 11 months and because the manic episode lasted 6.5 months. Ghadirian¹⁰ described 2 depressed patients (1 was bipolar) who developed hypomania 1–2 days after the rapid withdrawal of a TCA. In both patients, the symptoms spontaneously subsided within a week.

Corral et al.¹¹ described the development of transient mood elevation associated with antidepressant dose decrease in a woman with unipolar depression. This case was unusual for 2 reasons: the mood elevation was associated with a desipramine dose reduction (not withdrawal), and the finding was replicated. On the first occasion, the dose was reduced from 225 mg/day to 150 mg/day; improvement in mood occurred within 48 hours and lasted 3 days. The patient then relapsed into depression. The dose of desipramine was increased to 225 mg/day with no success. Two weeks later, the dose was deliberately reduced as before. There was again an improvement in mood within 48 hours; this time, the improvement lasted 9 days, after which the patient again relapsed into depression. An abrupt switch from desipramine to clomipramine did not result in mood elevation; apparently, clomipramine protected against desipramine-related withdrawal phenomena.

A depressed woman developed a 2- to 3-week hypomanic episode days after the tapered withdrawal of imipramine. The woman relapsed into depression after the abatement of the hypomania.³ A bipolar depressed woman was abruptly withdrawn from phenelzine and lithium because the drugs were ineffective. She developed hypomania 2 days later. The hypomania lasted only 5 days (and was hence unlikely to have been a true episode triggered by lithium withdrawal). The patient then relapsed into depression. She was prescribed imipramine, which, too, was ineffective. The imipramine was also abruptly withdrawn, leading again to hypomania 1 day later. This second episode of hypomania waned within a week of the addition of clomipramine. The patient attained euthymia and maintained the improvement for 3 months. When she relapsed into depression, clomipramine was abruptly withdrawn, but no hypomania supervened.¹²

Szabadi¹³ reported that a woman with obsessive-compulsive disorder (OCD) developed a 1-day, self-limiting hypomanic syndrome in association with withdrawal from fluvoxamine. Ceccherini-Nelli et al.¹⁴ described 1 schizophrenic patient and 9 depressed patients who were prospectively studied after the abrupt withdrawal of different antidepressant drugs. Two patients developed withdrawal hypomania: 1 had been receiving amitriptyline and the other, imipramine. Regrettably, the course and outcome of the syndromes were not described in the report.

Withdrawal mania was described in a bipolar woman who had abruptly stopped taking doxepin 6 weeks earlier. The switch was deemed to be drug-related rather than spontaneous because treatment with lorazepam (3 mg/day) and lithium (0.8 mEq/L) did not reduce the severity of the illness, whereas reintroduction of doxepin on day 13 after hospital admission led to marked improvement within 1 day. Lithium and lorazepam were tapered and withdrawn 4 weeks following admission, and the patient was discharged in a stable condition a fortnight later taking only doxepin (75 mg/day).¹⁵

MacCall and Callender¹⁶ reported the development of hypomania in a severely depressed, possibly bipolar woman who abruptly discontinued mirtazapine following 5 weeks of ineffective treatment. The hypomania developed within 2 days of drug discontinuation and lasted over 6 weeks. Benazzi¹⁷ reported the development of psychotic mania in a woman with bipolar II disorder who was gradually withdrawn from a low dose (50 mg/day) of sertraline following 2 years of treatment with the drug. The symptoms began a few days following drug discontinuation and remitted in 4 weeks with the help of neuroleptic drugs.

Only 2 studies have examined how common antidepressant-withdrawal mania really is. In the first study, Shriver et al.¹⁸ observed that 12 (15.2%) of 79 episodes of mania in 39 patients developed within 2 weeks of stopping antidepressant treatment. These 12 patients had received a selective serotonin reuptake inhibitor (SSRI; N = 7), a monoamine oxidase inhibitor (MAOI; N = 3), a TCA (N = 1), or a serotonin-norepinephrine reuptake inhibitor (N = 1).

In the second study, Goldstein et al.¹⁹ examined prospectively obtained data from 73 bipolar patients. Six patients (8.2%) developed antidepressant-withdrawal hypomania or mania 1-23 (mean = 13.5) days after starting the drug taper. The drugs had been discontinued because of euthymia (N = 2) or nonresponse to treatment (N = 4)after 4.5-44 (mean = 19) weeks of treatment. The withdrawn drugs were sertraline (N = 2), fluoxetine (N = 1), desipramine (N = 1), nortriptyline (N = 1), and venlafaxine (N = 1). The drug doses were in the moderate-to-high range in all but 1 patient. In 5 of the 6 patients, the withdrawal syndrome was dysphoric from the onset or was initially euphoric and turned dysphoric later. The mania was mild (hypomania) in only 1 patient. Only 1 patient experienced a concurrent physiological withdrawal syndrome as described by Zajecka et al.⁴ The mania lasted 12-49 (mean = 27.8) days and remitted spontaneously in 1 patient, with the reinstitution of venlafaxine in another patient, and with antipsychotic medication in the remaining 4 patients. Interestingly, the withdrawal mania developed even though all patients were receiving mood stabilizers (lithium, carbamazepine, valproate) alone or in combination.

The Goldstein et al.¹⁹ report is commendable because it is the only study in the literature to present comprehensive data on the patients involved. The report also attempted to determine whether the withdrawal mania could have been spontaneous, seasonal, or an antidepressant switch, and, hence, coincidental with rather than a result of antidepressant withdrawal. It appeared from the data that there was a possibility of antidepressant-induced mania in only 1 patient; this patient had received sertraline for only 4.5 weeks prior to drug discontinuation and the subsequent onset of mania. Finally, 2 of the 6 patients subsequently experienced antidepressant-withdrawal mania on each of 2 occasions of drug discontinuation.

In the most recent article, Ali and Milev²⁰ reviewed antidepressant-withdrawal mania in mood disorders and very briefly described a case of their own: that of an elderly bipolar man who developed mania 2 days after suddenly stopping nortriptyline. The mania abated after an unspecified period with the use of valproate and risperidone.

DISCUSSION

Although antidepressant drugs are prescribed for depression, panic disorder, OCD, phobic disorder, generalized anxiety disorder, chronic pain syndromes, and several other states, the literature on antidepressant-withdrawal hypomania or mania describes the syndrome almost exclusively in the context of adults with unipolar or bipolar disorder during depressed or euthymic phases. The only exception appears to be a woman with OCD who developed a 1-day hypomanic spell after the sudden withdrawal of fluvoxamine.¹³ There appear to be no reports of antidepressant-withdrawal mania in adolescents, in patients with schizophrenia or other psychiatric diagnoses, or in patients in whom an antidepressant with 1 spectrum of action was substituted for an antidepressant with another.

Could the descriptions of antidepressant-withdrawal mania reported in the literature actually be cases in which incipient mania was the cause of antidepressant withdrawal due to noncompliance? It is unlikely. In almost all of the reports reviewed in the previous section, the withdrawal of medication was a considered act initiated by the clinician, and the development of mania after antidepressant withdrawal was objectively recorded by the clinician. Could the reports be cases of mania occurring coincidentally with antidepressant withdrawal or cases of rapid-cycling induced by antidepressant drugs? These possibilities, too, are unlikely. In many cases, the patients had been taking the medication for years, or the withdrawal mania was brief and self-limiting, or the withdrawal mania waned with the reintroduction of the withdrawn drug, or the withdrawal mania recurred when the same or different drug was withdrawn after subsequent introduction.

Nosology

Three syndromes have been described in the antidepressant-withdrawal mania literature: mood elevation,¹¹ hypomania,¹⁶ and mania.¹⁹ Notwithstanding, many reports have used the general phrase "antidepressant-withdrawal mania" when the syndrome described appears to have been hypomanic in intensity. It is suggested that future reports differentiate between the 3 levels of severity. DSM-IV criteria²¹ can be used to differentiate between mood elevation (mood elevation and behavioral changes that do not meet DSM-IV criteria for hypomania), hypomania (meets all DSM-IV criteria for hypomania without requiring the duration criterion), and mania (meets all DSM-IV criteria for mania without requiring the duration criterion).

The correct diagnostic assignment would be substanceinduced mood disorder with manic features and with onset during withdrawal or, more specifically, antidepressantwithdrawal-induced mood disorder with hypomanic/ manic features (DSM-IV 292.84). However, the DSM-IV criteria in this section are too general for the specific con-

TADIE 1. SUPPESIEU DIAPHOSLIC CITIETIA IOI PIODU DIEVALION SVIULOTIES ASSOCIALEU WILH ATHIUEDIESSAIL WILHUTAWA	Table 1.	Suggested Diagnostic	Criteria for Mood Elevation	Syndromes Associated Wi	th Antidepressant Withdrawal
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Mood Elevation Syndrome Related to Antidepressant Withdrawal ^{b,c}	Mood Elevation Syndrome Unrelated to Antidepressant Withdrawal
1. The mood elevation begins AFTER sudden antidepressant withdrawal but within 2 weeks of the withdrawal.	 The mood elevation may occur more than 2 weeks after sudden antidepressant withdrawal.
2. There are no confounding factors, such as the simultaneous sudden discontinuation of lithium.	Confounding factors may be present, such as the simultaneous sudden discontinuation of lithium.
3. The syndrome is transient and self-limiting; the patient may relapse into depression.	The syndrome lasts several weeks or longer and may require antipsychotic or other medication for symptom relief.
4. The syndrome may respond to the reinstitution of the withdrawn antidepressant drug.	 The syndrome does not respond to the reinstitution of the withdrawn antidepressant drug.
5. The syndrome differs in symptoms, duration, and severity from previously experienced manic or hypomanic episodes.	The syndrome resembles previously experienced manic or hypomanic episodes in symptoms, duration, and severity.
^a The specification of mood elevation, hypomania, or mania would depend	upon degree: for hypomania and mania.

"The specification of mood elevation, hypomania, or mania would depend upon degree; for hypomania and mania, DSM-IV criteria may be applied without regard to the duration criterion.

^bIf antidepressant-withdrawal mood elevation is narrowly defined as a specific adverse reaction distinct from the repertoire of the subject's mood disorder, criteria 1 and 2 are necessary, along with at least 1 of the remaining 3 criteria.

"If antidepressant-withdrawal mood elevation is broadly defined to include a vulnerability to true mania or hypomania as

characteristic of the subject's bipolar illness, only criteria 1 and 2 are required.

text of antidepressant withdrawal. Therefore, 2 changes are suggested in addition to the duration modification specified previously: (1) The symptoms should develop during the period of drug washout (which will vary in duration, depending upon the half-life of the drug) or within an arbitrarily set period of 2 weeks of sudden drug discontinuation. (2) The distress/impairment criterion need not necessarily be met. Interestingly, DSM-IV lists a number of substances that when withdrawn may result in mood changes; the list does not include antidepressant drugs.

The nature of antidepressant-withdrawal mood elevation syndromes is a critical issue. Are these withdrawal phenomena, or are these true episodes that are triggered by antidepressant withdrawal? If the former, they will behave like other withdrawal phenomena in appearance, characteristics, and course; if the latter, they will resemble true episodes previously experienced by the patients. Regrettably, none of the studies identified in the literature formally differentiated the withdrawal syndromes experienced by the patients from their previous episodes of mania or hypomania (if any); however, most of the descriptions in the studies suggested that the episodes were atypical in at least some characteristics.

In this context, it must be considered that sudden antidepressant withdrawal may precipitate only a transient withdrawal syndrome in some patients, such as those with unipolar illness, and a full-blown switch into a true episode of hypomania or mania in other patients, such as those with bipolar illness. A clear idea regarding the accuracy of this suggestion could not be formed from the review of the literature because many reports did not clearly describe the polarity of the patients and because subsequent manic episodes may have changed the diagnosis of the illness from unipolar to bipolar disorder. In this context, one must consider that the bipolar I versus bipolar II distinction may also influence the expression and nature of the antidepressant-withdrawal manic syndrome. Table 1 suggests criteria that might be used to diagnose antidepressant-withdrawal mania. The table suggests how these criteria may be used to identify mania as a specific antidepressant-withdrawal syndrome (narrow criteria) as well as mania as a true episode induced by antidepressant withdrawal (broad criteria). The table additionally suggests differences between antidepressantwithdrawal mania and mania unrelated to antidepressant withdrawal.

Incidence and Differential Diagnosis

Only 1 study has attempted to systematically identify the risk of antidepressant-withdrawal mania. Goldstein et al.,¹⁹ using prospectively obtained data, found that 6 (8.2%) of 73 bipolar patients developed the syndrome during an antidepressant taper despite the concurrent use of mood stabilizers.

Antidepressant-withdrawal mania is clearly uncommon. Across the decades, hundreds of thousands of patients must have abruptly discontinued antidepressant drugs as a manifestation of poor drug compliance; yet, the reports of antidepressant-withdrawal mania are few. Goldstein et al.¹⁹ suggested that the rarity of description of the phenomenon in the literature may be due to episode misattribution and/or the protective effect of mood stabilizers. It is also possible that a mild and transient syndrome may not be reported or even recognized by a noncompliant patient. Prospective research is required to address the true incidence of the condition across drug and diagnostic categories. In this context, the differential diagnoses suggested in Table 2 must be kept in mind.

Predisposing Factors

The apparent rarity of antidepressant-withdrawal mania suggests that it develops idiosyncratically in vulnerable individuals. It remains to be determined whether this vulnerability is state-dependent, trait-dependent, or both. In this context, it is interesting that Corral et al.¹¹

Table 2. Differential Diagnoses of Antidepressant-Withdrawal Mania^{a,b}

- 1. Mania occurring before the antidepressant withdrawal, leading to antidepressant discontinuation as a manifestation of medication noncompliance.
- 2. Mania coincidentally developing shortly after the antidepressant withdrawal.
- ^aIn either of these situations, the mania may occur as part of the natural course of the illness, as a result of an antidepressant-induced switch, or as a result of antidepressant-induced rapid cycling.
- ^bAgitated depression and a physiologic withdrawal syndrome also have been described as potential mania-related confounds (see Goldstein et al.¹⁹).

described the recurrence of elevated mood after a second deliberate "challenge" of (relative) antidepressant withdrawal, whereas Goldstein et al.¹⁹ described recurrence of antidepressant-withdrawal mania on 2 subsequent occasions. Even more interesting is the report of withdrawal hypomania accompanying the abrupt discontinuation of phenelzine on 1 occasion, imipramine on a second occasion, but not clomipramine on a third occasion.¹²

Mechanisms

Four possibilities are considered to explain antidepressant-withdrawal mania.

Possibility 1. Most antidepressant drugs, particularly the TCAs, block cholinergic, noradrenergic, and/or sero-tonergic receptors. These receptors consequently upregulate.²² Sudden withdrawal of such antidepressant drugs would unblock the upregulated receptors, leading to a cholinergic, noradrenergic, and/or serotonergic overdrive. In susceptible patients, this overdrive could manifest as hypomanic symptoms.^{2,3,6,23}

Possibility 2. Possibility 1 neglects other potentially important changes associated with antidepressant therapy and withdrawal. After chronic treatment with a monoamine reuptake inhibitor, presynaptic and postsynaptic receptors which are not blocked by the antidepressant drug compensatorily down-regulate.²² Sudden withdrawal of the drug would then result in a sudden decrease in the synaptic availability of the monoamine neurotransmitter(s). Consequently, there would be a decreased autoreceptormediated inhibition of the presynaptic neuron and a decreased postsynaptic receptor-mediated stimulation of the postsynaptic neuron. The balance between the preand postsynaptic effects is unpredictable, which means that the net effect of sudden antidepressant withdrawal on neurotransmission (as modulated by these receptors) would also be unpredictable. Thus, sudden antidepressant withdrawal may result in increased neurotransmission through receptors that were up-regulated because of direct blockade by the drug (possibility 1) and unpredictable changes in neurotransmission through other receptors that were down-regulated by the drug. The net effect of sudden antidepressant withdrawal on synaptic neurotransmission is therefore complex; as a result, cholinergic overdrive, hyposerotonergic, noradrenergic, and other unitary hypotheses described elsewhere^{20,23} are probably simplistic. The complexity and unpredictability might explain the different patterns of and the variations in the susceptibility to mania withdrawal reactions in different patients, but this very complexity and unpredictability render the exact mechanism of antidepressant-withdrawal mania uncertain. Possibility 2 is thus a higher-level expression of possibility 1.

Possibility 3. A complicating factor in the search for mechanisms is the description of antidepressantwithdrawal mania across a wide range of antidepressant agents and hence a wide range of pharmacodynamic processes. This suggests that the search for mechanisms must eschew drug-specific processes and, instead, address processes that are common to all antidepressant classes. Thus, only a very general hypothesis can be advanced: that the sudden discontinuation of a drug that increases the availability of any of several neurotransmitters (and that may or may not block 1 or more neuroreceptors) may, in vulnerable individuals, activate a final common neuronal process that elevates mood. This final common pathway for the induction of antidepressant-withdrawal mania requires identification, as do the reasons for the idiosyncratic activation of this pathway in patients who develop withdrawal mania. If possibility 3 is true, possibilities 1 and 2 diminish in importance.

Possibility 4. As an alternative to possibility 3, it is conceivable that antidepressant-withdrawal mania may occur through different final pathways in different contexts. And, a combination of possibilities 1 and 2 might further explain the phenomenon: the mania arises through increased neurotransmission through certain receptors (possibility 1), and its unpredictable occurrence is due to the unpredictable modulation by other receptors (possibility 2).

Antidepressant-withdrawal mania, defined narrowly as a withdrawal syndrome, differs from true mania in several ways. For example, it is often brief ^{6,12,13} and may respond to the reinstitution of the withdrawn antidepressant drug,^{7,15,19} suggesting that the mechanisms of antidepressant-withdrawal mania differ significantly from the biological underpinnings of true mania. Alternatively, there may be no biological difference between the narrow and broad syndromes (Table 1); that is, the mechanisms idiosyncratically triggered by sudden antidepressant withdrawal may be the same in all patients who experience resultant mood elevation. However, the mood elevation syndrome may be limited in some patients, such as those with unipolar depression, and extended to full-blown hypomania or mania in other patients, such as those with bipolar disorder. This may explain why mania following antidepressant withdrawal was prolonged and required pharmacologic intervention in some reports.^{5,16,17}

SYNTHESIS

Antidepressant withdrawal has been associated with mood elevation,¹¹ hypomania,¹⁶ and mania.¹⁹ The syndrome has been associated with the withdrawal of TCAs,^{7,15} SSRIs,^{13,24} mirtazapine,¹⁶ venlafaxine,^{19,25} and MAOIs.^{12,26} There is no literature on withdrawal mania associated with antidepressants such as amineptine, tianeptine, amoxapine, and reboxetine.

The syndrome has been reported after the sudden withdrawal of antidepressant medication,⁶ tapered discontinuation,¹⁹ or even merely a decrease in dose.¹¹ The onset of the syndrome was reported as early as a day¹⁹ or as late as 6 weeks following drug discontinuation or taper¹⁵; the syndrome lasted as little as a single day¹³ to as long as over a month.^{16,19}

Antidepressant-withdrawal hypomania or mania so far has been described only in adults.¹⁹ Those affected have included unipolar depressed patients,⁵ bipolar depressed patients,¹⁹ and a patient with OCD.¹³ The syndrome has remitted spontaneously⁶ with the help of medication such as neuroleptics⁵ or even with the reinstitution of the withdrawn antidepressant drug.^{7,15,19} Concurrent mood stabilization with lithium, valproate, carbamazepine, or combinations thereof do not necessarily protect against the development of the syndrome.¹⁹

After recovery from antidepressant-withdrawal hypomania, patients have been reported to attain euthymia or relapse into depression.^{2,5,19} The syndrome has been replicated in the same patients during the same¹¹ or later¹⁹ episodes of depression.

Adrenergic hyperactivity⁶ and cholinergic overdrive associated with compensatory serotonergic and noradrenergic overdrive²³ are mechanisms suggested to explain the phenomenon, but there are many patients in whom these mechanisms are unsatisfactory because the syndrome has been described in states of potentially underactive adrenergic or serotonergic neurotransmission. It is very likely that some unknown state- or trait-dependent mechanisms, common to antidepressant classes, are activated in vulnerable patients.

The incidence of antidepressant-withdrawal hypomania and mania is unknown. Shriver et al.¹⁸ observed that 12 (15.2%) of 79 episodes of mania in 39 patients developed within 2 weeks of stopping antidepressant treatment. Goldstein et al.¹⁹ found that 6 (8.2%) of 73 bipolar patients developed withdrawal hypomania or mania during a tapered withdrawal of antidepressant treatment. The rarity of description of the phenomenon in the literature may be because of underrecognition due to mildness or transience, episode misattribution, and/or a protective effect of mood stabilizers. Prospective research is required to address the true incidence of the condition across drug and diagnostic categories with predefined criteria to distinguish between antidepressant-withdrawal mania and other states (Table 1). Differential diagnoses (Table 2) also must be kept in mind when considering antidepressant-withdrawal mania; these have been detailed by Corral et al.¹¹ and Goldstein et al.¹⁹

Clinicians should be aware of antidepressant-withdrawal mania because if it occurs when switching from 1 antidepressant drug to another, the mania may be mistaken for improvement, while if it occurs when the antidepressant drug is being withdrawn, the mania may be mistaken for a switch. The correct identification of antidepressant-withdrawal mania can lead to a more appropriate line of management, which would require 1 of the following: symptomatic treatment, because the syndrome is often self-limiting, or reinstitution of the withdrawn drug if the syndrome persists or if the patient relapses into depression.

Researchers who recruit manic patients (such as into clinical trials) should screen out patients with possible antidepressant-withdrawal mania. When it is difficult to decide whether the mania resulted from antidepressant withdrawal or whether the antidepressant withdrawal resulted from mania, the criteria described in Table 1 may need to be applied.

As a final note, patients who experience antidepressant-withdrawal mania do not necessarily have bipolar disorder^{5,13}; this has implications for both diagnosis and maintenance treatment.

A limitation of this study is that it depended upon an electronic search of only 1 database, PubMed. It is possible that searching other databases would have yielded more articles. To offset this limitation, the reference lists of identified articles were hand-searched for further relevant material; hand-searches of the indexes of leading psychiatry journals were also performed for the years 1998–2003. This study also retrieved more articles than did another recent review.²⁰

Drug names: amitriptyline (Elavil and others), carbamazepine (Carbatrol, Tegretol, and others), clomipramine (Anafranil and others), desipramine (Norpramin and others), doxepin (Sinequan and others), fluoxetine (Prozac and others), imipramine (Tofranil and others), lithium (Eskalith, Lithobid, and others), lorazepam (Ativan and others), mirtazapine (Remeron and others), nortriptyline (Aventyl, Pamelor, and others), phenelzine (Nardil), protriptyline (Vivactil), risperidone (Risperdal), sertraline (Zoloft), trazodone (Desyrel and others), venlafaxine (Effexor).

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