

Switch to Mania Upon Discontinuation of Antidepressants in Patients With Mood Disorders: A Review of the Literature

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Objective: To review the literature for reported cases of mania related to discontinuing antidepressant treatment, as well as for possible explanations of this phenomenon, and to present a case report.

Method: We undertook a literature review through the PubMed index, using the key words mania, antidepressant withdrawal, and antidepressants in bipolar disorder. We reviewed 11 articles featuring 23 cases. Where available, we noted and tabulated certain parameters for both bipolar disorder (BD) and unipolar depression. We use a case example to illustrate the phenomenon of mania induced by antidepressant withdrawal.

Results: For patients with unipolar depression, we found 17 reported cases of mania induced by antidepressant withdrawal. Antidepressants implicated included tricyclic antidepressants (TCAs) (12/17), monoamine oxidase inhibitors (MAOIs) (2/17), trazodone (1/17), mirtazapine (1/17), and paroxetine (1/17). For patients with BD, we found 19 reported cases of mania induced by antidepressant withdrawal, including our own case example. Of these, selective serotonin reuptake inhibitors (SSRIs) (10/19), TCAs (4/19), MAOIs (2/19), and serotonin norepinephrine reuptake inhibitors (SNRIs) (2/19) were implicated.

Conclusion: Our case report supports the observation of antidepressant withdrawal-induced mania in patients with BD. It is distinguishable from antidepressant-induced mania, physiological drug withdrawal, and mania as a natural course of the illness. Many theories have been put forward to explain this occurrence. Noradrenergic hyperactivity and “withdrawal-induced cholinergic overdrive and the cholinergic-monoaminergic system” are the 2 most investigated and supported models. The former is limited by poor clinical correlation and the latter by its applicability only to anticholinergic drugs.

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Clinical Implications

- This review will increase awareness of the phenomenon of antidepressant withdrawal-induced mania.
- This review furthers understanding of the significance of iatrogenesis in the course of bipolar disorder (BD) and may reduce the high frequency of starting and stopping various antidepressants.

Limitations

- Owing to the small sample size, we were not able to run statistical tests of significant power.
- There was a lack of good-quality demographic data.

Key Words: mania, antidepressant withdrawal, bipolar disorder

Antidepressants have a well-established role in the treatment of bipolar disorder (BD). There is also a known, inherent risk of antidepressant-induced mania in bipolar illness (as high as 35% [1]) that is accepted and considered in any treatment decision. However, a paradoxical shift to mania upon withdrawal of an antidepressant is not a commonly reported occurrence. Since 1981, there have been only 17 reports of antidepressant withdrawal-induced mania in patients with unipolar depression. Most cases involved the use of tricyclic antidepressants (TCAs). There were no such case reports in patients with BD until 1998, when 2 articles were published reporting similar observations in 18 patients. Most of these cases involved the use of selective serotonin reuptake inhibitors (SSRIs). Since 1999, there have been no other reported cases to support withdrawal mania in patients with BD. We present a review of the literature and provide a supporting case report of a patient with BD who had a clear manic episode precipitated by abrupt discontinuation of nortriptyline. It is our hope that, as further cases are identified and reported, the sample size will become large enough for meaningful interpretations of apparent risk factors and correlative factors, such as antidepressant class or possible predisposition according to sex.

Method

We undertook a literature review through the PubMed index, using the key words mania, antidepressant withdrawal, and antidepressants in bipolar disorder. Identified articles were reviewed, and demographic data were pooled and tabulated for unipolar depression and BD. Recorded parameters were as follows: patient diagnosis; age; sex; antidepressant type, antidepressant dosage, and length of treatment before withdrawal; abrupt (< 5 days) vs gradual (5 days to 8 weeks) antidepressant discontinuation; onset of manic symptoms from time of antidepressant withdrawal; management of manic symptoms; thyroid status; and family history of BD. Means were calculated for each parameter unless data were unavailable, in which case ranges were recorded. Using the same key words, we searched related articles for possible explanations. Each theory was explained mechanistically and assessed for strengths and limitations.

Literature Review Results

For patients with unipolar depression, we found 17 reported cases of mania induced by antidepressant withdrawal (2–10), 12 of which involved female patients. In 1 case, sex and age were not mentioned. Eliminating this study gave an age range of 21 to 65 years (mean 39 years) for female subjects and an age range of 18 to 50 years (mean 31.3 years) for male subjects. TCAs were implicated in 12 cases. Specifically, these included amitriptyline in 5 cases; imipramine in 2 cases; desipramine in 2 cases; and nortriptyline, protriptyline, and

doxepin in 1 case each. Monoamine oxidase inhibitors (MAOIs) (specifically, isocarboxazid) were implicated in 2 of the 17 cases. Of the remaining cases, 1 each involved trazodone, paroxetine, and mirtazapine. Because specific data were unavailable in some studies, it was difficult to calculate a true mean length of treatment. We therefore divided treatment length into 2 categories: ≤ 6 weeks and > 6 weeks, since antidepressant-induced mania is known to occur in the same time period that it takes for an antidepressant to have an effect (that is, 4 to 6 weeks). In 4/17 cases, antidepressant treatment was for 6 weeks or less, and in 13/17 cases treatment was for more than 6 weeks, with a range of 9 weeks to 19 years. Withdrawal was abrupt in 8/17 cases and gradual in 9/17. The average time to onset of manic symptoms was 3.9 days, with a single outlier occurring 7 weeks after abrupt discontinuation of doxepin 25 mg 3 times daily that had been taken for 19 years. Symptoms were managed by reinstating the antidepressant in 3/17 cases (specifically, desipramine in 2 cases and doxepin in 1 case), by starting antipsychotics in 3/17 cases, by starting antipsychotics and lithium in 2/17 cases, and by starting lithium alone in 1 of 17 case. Symptoms resolved spontaneously in 2/17 cases. Of the remaining cases, 3 refused treatment, symptom management was not reported in 2, and no treatment was necessary in 1 case. Family history was negative in 11/17 cases, positive in 2/17 cases, and not mentioned in 4/17 cases.

For patients with BD, a study by Goldstein and colleagues described 6 cases of antidepressant withdrawal-induced mania (11). Data on age and sex were not provided. SSRIs were implicated in 3/6 cases (specifically, sertraline in 2 cases and fluoxetine in 1 case). TCAs were implicated in 2/6 cases (specifically, 1 case each involving desipramine and nortriptyline). The last case implicated venlafaxine. Treatment length was 35 to 480 days, with a mean of 203 days (6.5 months). In 1 of the 6 cases, the treatment length was only 5 weeks, and the antidepressant was abruptly withdrawn in a single day. Withdrawal was gradual in the remaining 5 cases, with a mean taper length of 23.4 days and a range of 11 to 43 days. The average time to onset of manic symptoms was 13.5 days, with a range of 1 to 23 days. Symptoms were managed by antidepressant reinstatement in 1 case and by starting antipsychotics in 4 cases. In 1 case, symptoms were untreated. No information regarding family history of BD or thyroid status was provided in any of the 6 cases. Goldstein and colleagues refer to a finding by Shriver and others, who reported 12 such cases in a retrospective review presented at the 151st Annual APA meeting. However, apart from naming the classes of antidepressants implicated, they provide no further data from this report.

Our own case example (12) involved a 74-year-old man with a 30-year history of BD who had been on nortriptyline 100 mg

Table 1 Different types of mania compared

	Mania as a natural course of illness	Mania induced by antidepressant withdrawal	Antidepressant-induced mania	Physiological drug withdrawal
Time to onset of mania symptoms after antidepressant discontinuation	Variable, unrelated	> 8 weeks	Within 4 weeks in bipolar disorder (42) and 8 weeks in unipolar depression (43)	Abrupt onset (hours to days)
Length and severity of mania symptoms	Severe symptoms, last several weeks	As observed in various studies	Milder and briefer	Affective symptoms mild short-lived, less common; symptoms are primarily somatic (45)
Resolution of mania with antidepressant reinstatement	No	Yes	No	Yes, within 24 hours of reinstatement of antidepressant (46)
Method of symptom abatement	Mood stabilizers with or without antipsychotics, benzodiazepines	Reinstitution of antidepressant, mood stabilizers	Withdrawal of antidepressant, mood stabilizers	Symptoms abate within 1 day to 3 weeks of absence of antidepressant
Family history of bipolar disorder	Common	Not a common observation in studies thus far	Uncommon	Uncommon

^aGeneral somatic distress as described by Haddard and others includes gastrointestinal distress (abdominal pain, nausea, and diarrhea), sleep disturbance (insomnia, vivid dreams, nightmares), and somatic distress (sweating, lethargy, headaches). Affective symptoms are less common and are characterized by anxiety, irritability, and low mood.

daily for over 12 months. He abruptly stopped taking it and developed mania symptoms within 2 days. His symptoms were successfully treated with valproic acid 500 mg twice daily and risperidone 1.5 mg twice daily. He was known to be euthyroid, and his only psychiatric family history was that his mother suffered from depression.

When combined, the findings reported by Goldstein and colleagues (including those cited for Shriver and others) (11) and our own case report (12) yield the following data for implicated antidepressants: SSRIs in 10/19 cases, TCAs in 4/19 cases, MAOIs in 3/19 cases, and SNRIs in 2/19 cases.

Goldstein and colleagues considered several differential diagnoses to explain this phenomenon, including antidepressant-induced mania leading to antidepressant discontinuation, agitated depression, physiological withdrawal syndrome, and spontaneous mania as the natural course of the illness (11). When these potential confounders were evaluated, however, they were ruled out as differential diagnostic considerations. Mania associated with antidepressant withdrawal differs in several aspects from spontaneous mania or from antidepressant-induced mania. Table 1 provides some distinguishing features of each mania type, as observed by the reviewed reports; it may aid in identifying more cases.

Discussion

Our case example illustrates and supports the previous observations of a similar phenomenon in patients with BD. Further, when the pooled demographic data provided in Tables 2 and 3 are examined, it is interesting to note certain trends. For example, among patients with unipolar depression, mania induced by antidepressant withdrawal appears to occur more frequently with TCAs. Among patients with BD, however, it appears more frequently with the SSRIs. In addition, antidepressant withdrawal-induced mania seems to occur more frequently in female patients with unipolar depression than it does in male patients. (Unfortunately, information on sex was not available for the study population with BD.) These findings are interesting, but thus far anecdotal. They may provoke some questions regarding the establishment of possible risk factors for developing this condition when enough reported cases exist for a sufficiently large sample size.

Several hypotheses have been postulated to explain the pathophysiology of antidepressant withdrawal-induced mania. They include a cholinergic-monoaminergic interaction hypothesis (13,14), hyposerotonergic mania (15), noradrenergic hyperactivity (2,10,16), rapid eye movement (REM) sleep rebound (4,17–19), and hyperdopaminergic mania (9).

Table 2 Pooled demographic data from studies of withdrawal mania in bipolar disorder

Study	Age, sex, family history	Mood stabilizer	Lithium level (mmol/L)	Antidepressant, daily dosage (mg) and length of treatment (weeks)	Gradual vs abrupt withdrawal (days)	Time to onset of symptoms (days)	Symptoms
Goldstein and others (11)	na	Lithium, carbamazepine	1.1	Sertraline, 200 x 12	Gradual (11)	11	Moderate mania
		Lithium, carbamazepine	1.0	Fluoxetine, 70 x 17	Gradual (43)	23	Moderate mania
		Lithium	1.0	Desipramine, 450 x 44	Gradual (20)	20	Moderate mania
		Lithium, valproic acid	0.5	Venlafaxine, 150 x 20	Gradual (29)	13	Moderate mania
		Lithium	1.1	Nortryptiline, 50 x 17	Gradual (14)	13	Hypomania
		Lithium	1.0	Sertraline, 150 x 4.5	Abrupt (1)	1	Moderate mania
Shriver and others (11)	na	na	na	SSRIs, 7 patients MAOIs, 3 patients TCAs, 1 patient Venlafaxine, 1 patient	na	na	na
Ali and others (12)	74-year-old man; mother had depression	none	Not applicable	Nortryptiline, 100 x 52	Abrupt (1)	2	Mania

MAOIs = monoamine oxidase inhibitors; SSRIs = selective serotonin reuptake inhibitors; TCAs = tricyclic antidepressants

The Cholinergic–Monoaminergic Interaction Hypothesis

The cholinergic–monoaminergic interaction model proposed by Dilsaver and colleagues (13,14) is one of the most studied hypotheses. Because of the antimuscarinic properties of TCAs, chronic administration leads to increased cholinergic receptor sensitivity in both the cholinergic-inhibitory and the monoaminergic-activating systems. This in turn reduces the sensitivity of such monoaminergic receptors as the dopaminergic and noradrenergic receptors. Withdrawing the antidepressant therefore precipitates cholinergic overdrive, thus activating the cholinergic–monoaminergic system, which acts to maintain homeostatic balance. Thus, in response to cholinergic overdrive, the monoaminergic synthetic pathways are activated; a measurable significant increase in tyrosine hydroxylase (the enzyme catalyzing the rate-limiting step in catecholamine synthesis) has been reported (14). Once the cholinergic overdrive abates, the monoaminergic system usually downregulates in parallel. In some patients, however, the system fails to downregulate, resulting in a state of relative monoaminergic excess and associated hypomania or mania. Although much evidence supports this hypothesis, it does not apply to drugs with weak anticholinergic properties, such as trazodone and MAOIs. Perhaps, in addition to the

cholinergic–monoaminergic interaction, some other mechanism causes similar activation upon withdrawal of weak anticholinergic drugs.

Hyposerotonergic Mania

The hyposerotonergic mania proposed by Zajecka and colleagues (15) applies to any antidepressant that potentiates, by whatever mechanism, the net concentration of serotonin in the synaptic cleft. TCAs, SSRIs, SNRIs, and trazodone all increase serotonin by blocking the presynaptic serotonin reuptake receptor. MAOIs increase serotonin by preventing its degradation by monoamine oxidase-A. The relative increase in serotonin in the synaptic cleft is thought to downregulate the postsynaptic serotonin receptors after prolonged exposure to antidepressants. Once the antidepressant is withdrawn, the presynaptic serotonin reuptake receptor is no longer blocked, leading to rapid reuptake of serotonin and a decreased concentration in the synaptic cleft. In the case of MAOIs, the degradation of serotonin is no longer blocked, again leading to its decreased concentration in the synaptic cleft. The reduction in serotonin leads to acute upregulation of the postsynaptic serotonin receptors, which then increases serotonin transmission through neuronal circuits and therefore

Table 3 Pooled demographic data from studies of withdrawal mania in unipolar depression

Study	Age and sex	Antidepressant daily dosage (mg) and length of treatment	Gradual vs abrupts withdrawal	Time to onset of symptoms	Symptoms	Family history of bipolar disorder
Mirin and others (2)	Ages not mentioned 6 women, 1 man	Amitryptiline, 200 (4 patients) Amitryptiline, 25 Imipramine, 200 Protryptiline "low dosage" treatment 3 months to 4 years	Abrupt: 3 (< 1 week) Gradual: 4 (2–8 weeks)	All occurred within 1 week	Hypomania and mania (not further quantified in study)	Negative in all 7 patients
Ghadirian (3)	35-year-old woman	Norytryptiline, 150 x 1 month with lithium 900 for augmentation	Abrupt	24 hours	Euthymia	Strong positive family history
McGrath and others (4)	Not mentioned	Imipramine unknown dosage x 6 weeks	Not mentioned	Not mentioned	Hypomania	Not mentioned
Theilman and others (5)	33-year-old woman	Trazodone, 300 x 4 months	Gradual (8 weeks)	7 weeks	Frank mania	Not mentioned
Callender and others (6)	65-year-old woman	Mirtzapine, 30 x 5 weeks	Abrupt	2 days	Mild hypomania	Not mentioned
Landry and others (7)	33-year-old woman	Paroxetine, 50 x 9 months	Abrupt	4 days	Mania and somatic distress ^a	Negative
Galynker and others (8)	59-year-old woman	Doxepin, 75 x 19 years	Abrupt	6 weeks	Mania	Not mentioned
Rothschild (9)	32-year-old woman	Isocarboxaid, 20 x 12 weeks	Abrupt	5 days	Mania	Negative
	26-year-old man	Isocarboxaid, 60 x 9 weeks	Gradual	3 days	Mania	Negative
Nelson and others (10)	18-year-old man	Desipramine, 250 x 4 months	Gradual	24 hours	Mania	Positive
	50-year-old man	Desipramine, 200 x 4 months	Unknown	36 hours	Mania	Negative

^aThis patient had nausea, diarrhea, abdominal cramps, chills, and dizziness

increases the neuronal firing rate. This is thought to be the final pathway in the development of hyposerotonergic mania. The hypothesis, however, has yet to be investigated.

Noradrenergic Hyperactivity

To explain several observations of a TCA-withdrawal syndrome, Charney and colleagues provided evidence for noradrenergic hyperactivity following abrupt discontinuation of TCAs in 7 patients with unipolar depression (16). In these subjects, they demonstrated urinary and plasma increases in 3-methoxy-4-hydroxyphenylethylene glycol (MHPG), reflecting increased norepinephrine turnover. They measured an increase in plasma and urinary MHPG of 26% and 39%, respectively, 1 week after TCA discontinuation and an increase of 74% and 61%, respectively 2, weeks after TCA discontinuation. Despite these clear elevations in plasma and urinary MHPG, only 1 patient demonstrated hypomanic behaviour as well as anxiety with panic attacks; 1 patient

demonstrated increased anxiety that did not correlate with daily changes in MHPG; 1 patient's depression improved; and the rest showed no change. Therefore, MHPG levels may not correlate as well as expected with symptomatology.

Rapid Eye Movement (REM) Sleep Rebound

There have been several studies in both animals and humans that demonstrate high voltage slow wave patterns characteristic of non-REM sleep in response to high dosages of atropine and other anticholinergic agents (2,20–38). This is in contrast to cholinergic agents, which promote REM sleep. REM sleep is known to be accompanied by increased cortical release of acetylcholine (39) that is temporally associated with EEG desynchronization and behavioural arousal (14). Thus, the spontaneous withdrawal of an anticholinergic agent is expected to cause a rapid rebound of REM-stage sleep. McGrath and colleagues have proposed that the increased REM sleep can be "sufficient to cause either a reduction in total sleep time

or at least a diminution of slow wave sleep, both of which have been reported to be associated with relief of depression and the precipitation of mania or hypomania" (4,18,19). Once again, this does not explain the precipitation of mania upon withdrawal of drugs with weak anticholinergic activity.

Hyperdopaminergic Mania

Some studies suggest that chronic treatment with MAOIs induces a subsensitivity of dopamine autoreceptors (40,41) and that such treatment therefore acts as an agonist to the dopamine autoreceptor, inducing a state of low dopamine. Rothschild proposed the opposite effect when the MAOI is withdrawn: loss of the agonist autoreceptor effects should lead to hyperdopaminergia, owing to decreased uptake of dopamine by the autoreceptor (9). He further pointed out that this mechanism would account not only for MAOI-withdrawal mania but also for mania seen after discontinuation of TCAs, as well as for the psychosis and paranoia seen after amphetamine withdrawal, since they are both also known to induce a subsensitivity of the dopamine autoreceptors (41).

Conclusions

Antidepressant withdrawal-induced mania is an interesting phenomenon distinct from antidepressant-induced mania or physiological drug withdrawal. It does not appear to coincide with the natural course of BD. Withdrawal-induced cholinergic overdrive and the action of the cholinergic-noradrenergic system remains the most investigated hypothesis for explaining antidepressant withdrawal-induced mania. In summary, this hypothesis proposes that, upon cholinergic overdrive, the monoaminergic synthetic pathways are activated in an effort to maintain homeostatic balance. Once the cholinergic overdrive abates, the monoaminergic system usually downregulates in parallel. In some patients, the system fails to downregulate, leading to a state of relative monoaminergic excess and associated hypomania or mania. However, this hypothesis is limited by its inability to explain similar observations involving antidepressants with weaker anticholinergic activity. If there were a way of predicting with some certainty which patients might be at risk for mania induced by antidepressant withdrawal, we could potentially prevent it. For example, it was interesting to note the higher proportion of patients on TCAs and of female patients affected. Its occurrence implies a higher incidence of diagnosing BD and, therefore, of treatment with mood stabilizers. With increasing reports of this phenomenon, it may be possible to develop its relation to some of the reported parameters.

There is a strong suggestion that the constant switching of antidepressants in patients (iatrogenesis) may induce rapid cycling in the population with BD. This leads to several

questions regarding the population with unipolar depression. After observing an episode of withdrawal mania in a patient previously diagnosed with unipolar depression, one wonders whether the diagnosis should be changed to BD, what would be the risk of another manic episode, and what may be the treatment implications for mood stabilizers. In addition, the question arises of whether reinstating the antidepressant is sufficient treatment. Long-term follow-up studies investigating the stability of the diagnosis over time are required to answer many of these questions. Depending on the results of such studies, iatrogenesis may become a new inclusion as an etiological factor in BD.

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Résumé : Le passage à la manie après interruption des antidépresseurs chez les patients souffrant de troubles de l'humeur : une analyse de la documentation

Objectif : Chercher dans la documentation des cas déclarés de manie liée à l'interruption du traitement aux antidépresseurs ainsi que des explications possibles de ce phénomène, et présenter une étude de cas.

Méthode : Nous avons entrepris une analyse de la documentation à l'aide de l'index PubMed, en utilisant les mots clés manie, antidépresseur, sevrage, et antidépresseurs du trouble bipolaire. Nous avons examiné 11 articles présentant 23 cas. Quand c'était possible, nous avons noté et totalisé certains paramètres tant pour le trouble bipolaire (TB) que pour la dépression unipolaire. Nous utilisons un exemple de cas pour illustrer le phénomène de la manie induite par le sevrage d'antidépresseur.

Résultats : Chez les patients souffrant de dépression unipolaire, nous avons trouvé 17 cas déclarés de manie induite par le sevrage d'antidépresseur. Les antidépresseurs en cause comprenaient des antidépresseurs tricycliques (ATC) (12/17), des inhibiteurs de la monoamine oxydase (IMAO) (2/17), de la trazodone (1/17), de la mirtazapine (1/17) et de la paroxétine (1/17). Chez les patients souffrant de TB, nous avons trouvé 19 cas déclarés de manie induite par le sevrage d'antidépresseur, y compris notre propre exemple de cas. Parmi ceux-ci, les inhibiteurs spécifiques du recaptage de la sérotonine (ISRS) (10/19), les ATC (4/19), les IMAO (2/19), et les inhibiteurs du recaptage de la sérotonine et de la noradrénaline (IRSN) (2/19) étaient en cause.

Conclusion : Notre étude de cas appuie l'observation de manie induite par le sevrage d'antidépresseur chez les patients souffrant de TB. Elle se distingue de la manie induite par un antidépresseur, du sevrage de médicament physiologique et de la manie dans le cours naturel de la maladie. De nombreuses théories ont été mises de l'avant pour expliquer cette manifestation. L'hyperactivité noradrénergique et « la surexcitation cholinergique induite par le sevrage et le système cholinergique-monoaminergique » sont les deux modèles les plus recherchés et soutenus. Le premier est limité par une mauvaise corrélation clinique et le deuxième, par son applicabilité réservée aux anticholinergiques.