

## Review Article

# Antidepressant-induced mania: an overview of current controversies

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**Objective:** The prevalence, characteristics, and possible risk factors associated with antidepressant-induced mania remain poorly described. The present review sought to identify published rates of antidepressant-induced mania and describe risk factors for its emergence.

**Methods:** A MedLine search was conducted of journals that focused on mania or hypomania associated with recent antidepressant use. Data from published reports were augmented with relevant findings from recent clinical trials presented at scientific conferences.

**Results:** Antidepressant-induced manias have been reported with all major antidepressant classes in a subgroup of about 20–40% of bipolar patients. Lithium may confer better protection against this outcome when compared with other standard mood stabilizers, although switch rates have been reported with comparable frequencies on or off mood stabilizers. Evidence across studies most consistently supports an elevated risk in patients with (i) previous antidepressant-induced manias, (ii) a bipolar family history, and (iii) exposure to multiple antidepressant trials.

**Conclusion:** About one-quarter to one-third of bipolar patients may be inherently susceptible to antidepressant-induced manias. Bipolar patients with a strong genetic loading for bipolar illness whose initial illness begins in adolescence or young adulthood may be especially at risk. Further efforts are needed to better identify high-vulnerability subgroups and differentiate illness-specific from medication-specific factors in mood destabilization.

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The relative risks and benefits of using standard antidepressant drugs for bipolar depression have become an increasing point of debate. Ever since Wehr and Goodwin's observations that tricyclic antidepressants could induce manias or hypomanias (1) and worsen the course of bipolar illness by accelerating cycle frequency (2), controversy has focused on a number of key areas regarding the treatment of bipolar depression. These include (i) reliable estimates of the incidence of antidepressant-induced mania, as distinguished from spontaneous cycling in the natural course of illness, (ii) debate about possible neurophysiologic mechanisms that could underlie polarity switches triggered by antidepressants, (iii) identifying clinical

predictors or risk factors for the phenomenon, (iv) determining the extent to which tricyclic antidepressants carry an elevated risk for manic inductions when compared with other, newer antidepressant drugs [such as selective serotonin reuptake inhibitors (SSRIs), serotonergic/noradrenergic reuptake inhibitors (SNRIs), or bupropion], and (v) clarifying the degree to which mood stabilizers effectively prevent antidepressant-induced manias. Little empirical data presently exist to help shed light on the extent and predictability of these risks, which stand alongside concerns about the under treatment of depression and persistently elevated suicide rates among bipolar patients (3).

This review will synthesize current information about the phenomenology of antidepressant-induced mania, in conjunction with the related phenomenon of changes in polarity from a unipolar to bipolar diagnosis. Findings are summarized from a MedLine search of journals based on the key terms 'antidepressant,' 'mania' and 'bipolar disorder.' This search was augmented with findings known to the authors from pertinent book chapters and unpublished empirical studies presented at major scientific conferences.

### Estimates of prevalence

Early descriptions by Goodwin and Jamison (4) broadly described the risk of antidepressant-induced mania in a wide range of bipolar patients (30–70%), although more contemporary estimates project this range as being closer to 20–40% of bipolar patients. These include 35% of 61 patients studied by Altshuler et al. (5); 28% of 79 patients in naturalistic treatment reported by Boerlin et al. (6); 27% of 44 patients drawn from a clinic population reported by Henry et al. (7); 40% of 53 patients studied at the Bipolar Disorders Research Clinic of the New York Presbyterian Hospital as reported by Goldberg and Whiteside (8); and 45% of 353 entrants to the multi-site National Institute of Mental Health (NIMH) Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) studied by us (9).

Notably, most contemporary estimates of antidepressant-induced mania are based on relatively small sample sizes drawn from naturalistic observations, rather than by randomized protocol assignment, introducing potential selection biases that could influence outcomes. Such studies nevertheless help to provide a framework from which to obtain initial estimates and generate hypotheses about the nature and scope of this clinical phenomenon. Furthermore, it is important to bear in mind that assumptions about polarity switches catalyzed by medications must be interpreted alongside an understanding of the natural history of spontaneous polarity switches in bipolar disorder. For example, Lewis and Winokur (10) found higher switch rates during psychiatric admission in patients receiving no somatic treatment (41%) when compared with patients who received electroconvulsive therapy (22%), monoamine oxidase inhibitors (25%), or tricyclic antidepressants (28%), however their retrospective chart review design limits interpretation of these findings. Life Chart data reveal that cycling patterns may vary idiosyncratically across individuals at various phases of their illness (11). Therefore, clinicians may

recognize departures from baseline cycle patterns and frequencies more confidently when such historical information is available.

It is further possible that a subgroup of bipolar patients exists that is particularly susceptible to mood destabilization by antidepressants. Such patients may experience inductions of mania across multiple successive antidepressant trials. Goldberg and Whiteside (8) identified lifetime antidepressant-induced manias as the outcome for 26 of 164 individual antidepressant trials (16%) among 53 bipolar patients. In the total group who had antidepressant-induced manias, 19% had this outcome on two or more separate occasions. Similarly, multiple antidepressant-induced manias were evident in 15 of 29 bipolar patients (52%) studied by Boerlin et al. (6). Prevalence rates for the induction of mania across published antidepressant studies that report this outcome are summarized in Table 1.

### Implications about pathophysiology

A number of theoretical perspectives can be described in attempting to understand the etiology and pathophysiologic basis of antidepressant-induced manias. These may be summarized as follows:

#### Secondary mania

Uncertainty persists about whether antidepressant-induced mania represents a *bona fide* form of mania versus an iatrogenic side effect of drug therapy (perhaps dose-related, and presumably remediable by drug cessation without necessarily the need for long-term treatment). This latter view has been applied to other pharmacotherapies known to cause drug-induced changes in mood, cognition and/or behavior (e.g. steroids). Manias secondary to toxic-metabolic or drug-induced states in this sense are generally viewed more as adverse drug events rather than indicators of a bipolar diathesis; secondary manias typically resolve after drug cessation with time-limited symptomatic management as needed (12, 13). This perspective is reflected in DSM-IV, in which antidepressant-induced manias are classified not as a subtype of bipolar illness, but as a substance-induced mood disorder. This conceptualization contrasts with views described in DSM-III-R, in which mania induced by antidepressant treatment (medication or ECT) is considered a *bona fide* manic episode.

#### Revealing a bipolar diathesis

An alternative hypothesis involves the view that antidepressant-induced mania may reveal a bipolar

Table 1. Reported switch rates of antidepressant-induced mania from clinical trials in bipolar depression that report switch rates

Authors	Medication	n	Study duration	Mean dose (mg/day)	Switch rate (%)	Comments
Fogelson et al. (71)	Bupropion	11	6 weeks	286	54.5	Preexisting lithium and carbamazepine or valproate in five of six patients who switched
Sachs et al. (81)	Bupropion	9	8 weeks acute, 1-year continuation	358	11.0	Cotherapy with lithium, valproate or carbamazepine
Erfurth et al. (92)	Desipramine	10	4 weeks	140	30.0	Bupropion was added to diverse combination therapies in a treatment-refractory group
	Bupropion	13		286.5	0.0	
Himmelhoch et al. (77)	Tranlycypromine	16	6 weeks	37	21.0	No concomitant mood stabilizers used
	Imipramine	16		246	25.0	
Thase et al. (93)	Tranlycypromine	12	4–12 weeks	39	17.0	Double-blind crossover of non-responders from a prior tranlycypromine versus imipramine study (77)
Silverstone et al. (85)	Imipramine	4	8 weeks	242	25.0	'Switch' defined as YMRS >10
	Moclobemide	78		450–750	3.7	
	Imipramine	78		150–250	11.0	
Baldassano et al. (70)	Paroxetine	20	8 weeks	23	5.0	One patient on lithium plus carbamazepine developed hypomania
Vieta et al. (94)	Paroxetine	30	6 weeks	32	3.0	Open label, randomized. Paroxetine–venlafaxine switch rates numerically but not statistically different
Nemeroff et al. (83)	Venlafaxine	30	10 weeks	179	13.0	Two of three imipramine patients, and both placebo patients, who developed hypomania, had subtherapeutic serum lithium levels
	Paroxetine	35		32.6	6.7	
Kupfer et al. (95, 96)	Imipramine	39	8 weeks acute, then 16-weeks continuation	166.7	7.7	All subjects took therapeutically dosed lithium, valproate or carbamazepine
	Citalopram	45		34.5	6.7	
Cohn et al. (97)	Fluoxetine	30	3–6 weeks	62.3	0.0	Concurrent lithium in about 20%; 16% of imipramine- or placebo-non-responders who then took fluoxetine became hypomanic
Young et al. (84)	Imipramine	30	6 weeks	36	7.0	All subjects initially took lithium or valproate, to which study drug was then added
	Placebo	29			3.0	
	Paroxetine	11			0.0	
	Lithium or valproate	16			6.3	

diathesis [or first predisposing event, analogous to Knudson's (14) two-hit of two-mutational hypothesis for the initiation of neoplasia in genetically vulnerable individuals]. In this model, antidepressant-induced mania occurs solely among individuals with a preexisting constitutional susceptibility to bipolar illness. As such, it would represent one of several likely environmental factors capable of evoking the switch process from depression to mania or hypomania, such as circadian dysrhythmias [e.g. sleep deprivation (15), the crossing of time zones (16)], or the persistence of a *de novo* affective or psychotic disorder in the aftermath of psychoactive substance misuse. This view is consistent with the suggestion that individuals who

develop an antidepressant-induced mania may be more likely than not to subsequently have spontaneous manias or hypomanias (17). Although many clinicians have the impression that patients with a history of antidepressant-induced mania are more likely to go on to have subsequent spontaneous manias or hypomanias, no controlled data are available to confirm or refute this impression.

Behavioral sensitization

Models of kindling and behavioral sensitization have been proposed to explain the propagation of multiple episodes in bipolar disorder (18, 19). In as much as some psychoactive substances can

destabilize mood (e.g. alcohol) and hasten affective relapse (20), antidepressant drugs could constitute a similar pharmacologic influence that could accelerate relapses by increasing cyclicality. Such hypotheses are consistent with double-blind, placebo-controlled findings by Wehr and Goodwin (21), which demonstrate reversible rapid cycling induced by tricyclic antidepressants in about half of bipolar patients identified with rapid cycling. In this sense, the longitudinal concept of cycle acceleration is closely linked with the cross-sectional phenomenon of induction of mania by antidepressants.

#### Abrupt alterations in homeostasis

It is possible that either the introduction or elimination of antidepressant medications could cause destabilization of mood. For example, Goldstein et al. (22) reported a series of six cases of mania that occurred in the first 2 weeks after discontinuing SSRIs ( $n = 3$ ), tricyclics ( $n = 2$ ), or an SNRI ( $n = 1$ ), despite concomitant mood stabilizers. Such phenomena could relate to a physiologic withdrawal syndrome [particularly insomnia (23)] or to cholinergic or catecholaminergic changes caused by long-term antidepressant use preceding withdrawal. Thus, because of changes in catecholamine and indoleamine receptor sensitivity during chronic antidepressant treatment, abrupt discontinuation may lead to a relative depletion in these transmitter systems, theoretically resulting in hypomania (24, 25).

#### Genetic considerations

Family-genetic factors may hold particular importance in discriminating depressed patients at high vulnerability for either spontaneous manias or for antidepressant-induced mania. Some family-pedigree studies suggest that with regard to familial transmission, bipolar and unipolar probands may represent severe and mild forms of the same underlying disorder, respectively (26). In a study of 68 juvenile offspring or siblings of bipolar patients, over half showed signs of bipolarity during a 3-year prospective follow-up (27). Blacker et al. (28) evaluated characteristics in the unipolar-depressed relatives of bipolar versus unipolar probands and found that depressed relatives of bipolar patients had a higher rate of subthreshold bipolar features and a lower prevalence of panic symptoms, as well as numerically fewer depressive symptoms. Klerman (29) classified such depressed patients with a bipolar family history (but no personal history of mania or hypomania) as 'bipolar type V.' This clinical subgroup has

received relatively little empirical study with regard to episode frequency, clinical course, or treatment outcome with standard antidepressants versus mood stabilizers.

#### Symptom clusters across diagnoses

A final consideration that bears on both pathophysiology and nosology involves the relative limitations of conceptualizing bipolar disorder as a categorical diagnosis rather than as a constellation of varied dimensions of psychopathology. As described by Blacker and Tsuang (30), overlapping features of bipolar disorder with other syndromes such as borderline personality disorder (sharing mood instability), attention deficit-hyperactivity disorder (sharing distractibility and agitation) and schizophrenia (sharing psychosis) may indicate that subthreshold manifestations of bipolar illness could arise among depressed (or other) patients initially identified with psychiatric disorders other than bipolar illness. To the extent that antidepressant exposure may constitute one means by which to evoke a bipolar diathesis, 'switch' processes caused by antidepressants may not necessarily encompass a classical or even fully syndromal form of the illness. Related to this is the need for better means to discriminate stimulation effects of antidepressants (31) from subsyndromal manias.

In further support of this possibility, Levy et al. (32) observed antidepressant-induced manias in five of 167 consecutive anxiety disorder patients (3%), all of whom had cluster 'B' personality disorder comorbidities. These authors suggested that subthreshold, non-pathognomonic features related to bipolar illness, such as mood instability, might predispose to antidepressant-induced mania even among individuals without a primary mood disorder. Antidepressant-induced mania has also been recognized among patients with obsessive-compulsive disorder (OCD) (33). For example, Berk et al. (34) observed new-onset mania in five patients with OCD shortly after starting treatment with clomipramine, fluoxetine, or citalopram; the authors suggest a possible pathophysiologic link between bipolar illness and OCD based on this treatment outcome – a speculation consistent with other reports of overlap between these two disorders (35).

#### Unipolar to bipolar polarity conversions

In so far as depression is often the presenting feature of bipolar illness (36), uncertainty persists about the extent to which initially depressed patients are at risk for eventual conversions to

Table 2. Clinical and demographic predictors of unipolar to bipolar polarity conversion

Feature	Supportive evidence	Contrary evidence
Gender	None reported	Comparable male:female risk (8, 48)
Early age at onset	Eventual bipolarity more common if first depression is prepubescent (50), or occurs before about age 25 (40, 48), 30 (98), or 40 (41).	None reported
Substance abuse/dependence	None reported	Comparable risk if present or absent (8)
Psychosis at index depression	Significantly more psychotically depressed patients may later become bipolar than remain unipolar (range: 27–75%) (8, 40, 48, 52)	None reported
Bipolar family history	Initially depressed patients who eventually become bipolar appear more likely to have a bipolar family history (range: 17–75%) (8, 40, 48, 51)	None reported
Hyperthymic temperament	Temperamental features may be associated with eventual polarity conversions (especially from depression to bipolar II) (43, 47)	

bipolarity. Early estimates of this switch phenomenon – largely from a time in which available antidepressants (mostly tricyclics and monoamine oxidase inhibitors) were used less widely than in the more contemporary era – suggest that little more than 5–10% of initially depressed patients have a subsequent bipolar course (37–40). However, many previous studies focused on heterogeneous groups of both hospitalized and non-hospitalized depressed patients, and many included subjects already beyond the age at which polarity conversions are likely to have already occurred. Some cross-cultural studies have yielded findings at variance with earlier US studies, as suggested by a 39% switch rate from unipolar to bipolar diagnoses among 109 initially depressed patients from Madurai, India, followed for up to 13 years (41).

Table 2 summarizes clinical features described in the current literature as correlates of polarity switch from initial unipolar depression to mania or hypomania. Early age at onset of affective illness, bipolar family history, and severity of initial depression (e.g. psychosis, melancholia, and hospitalization) appear to hold particularly robust importance in gauging the likelihood of eventual polarity conversions. In addition to these characteristics, temperamental features among some affective disorder groups may predict eventual polarity outcomes. Perugi et al. (42) found that 72% of patients with atypical depressive features had bipolar II or other ‘soft spectrum’ characteristics, and among that subgroup, nearly 60% had antecedent hyperthymic or cyclothymic temperaments (in contrast to more socially phobic, non-histrionic, avoidant traits among those without bipolar features). Related trait characteristics linked with eventual switches to bipolar II diagnoses include constructs described by Akiskal et al. (43) such as mood lability, energy-activity

and daydreaming. The concept of pseudounipolar depression as originally described by Mendels (44) and subsequently others (43, 45, 46) bears importantly on this issue. Several clinical features linked to bipolarity may pertain to individuals who present initially with depression, including high recurrence rates (17, 27), hyperthymic temperamental features (47), and a family history of bipolar disorder (48).

Some authors have placed special importance on prepubescent mood disorders as denoting a likely pre-bipolar subtype of mood disorder (49, 50). Thus, follow-up studies of depressed or dysthymic adolescents have reported bipolar outcomes in 20–40% of subjects (51, 52). Early age at onset, in turn, has been linked with numerous biological and clinical outcome dimensions of bipolarity. For example, family pedigree studies suggest that age at onset may successively decline across multigenerational bipolar groups, consistent with the notion of genetic anticipation in a high-severity patient subgroup (53–55). Early-onset mood disorder patients who develop a bipolar course may be especially prone to have substance abuse comorbidity (20), mixed states or major depressions with hypomania (56, 57), more extensive and severe depressions (58), increased latency to diagnosis and mood stabilizer initiation (59), axis I comorbidities (60), psychosis (61, 62), neurodevelopmental deficits (63), suicidality (64, 65), and poorer functional outcome (66). In this regard, mood destabilization by antidepressants can be viewed as having a direct adverse impact on the course and outcome of bipolar disorder.

#### Predictors of antidepressant-induced mania

Existing reports that focus on antidepressant-induced mania have identified a limited number

of associated clinical features. Altshuler et al. (5), studying 51 bipolar inpatients, found no obvious risk factors related to inductions of mania after antidepressant use *per se*, although the related phenomenon of cycle acceleration attributable to antidepressant use (observed in 26% of eventual rapid cyclers) was linked with female gender, bipolar II subdiagnoses, and a greater number of previous antidepressant trials. Among the 21 of 53 bipolar patients who had antidepressant-induced manias in the Cornell Bipolar cohort (8), switches into mania or hypomania were more likely to have occurred in those with a history of drug or alcohol abuse/dependence (43% versus 18% in those without substance misuse;  $p = 0.005$ ), as well as among patients who had a greater number of antidepressant trials per year (0.20 annual trials in those who switched versus 0.12 annual trials in those who did not;  $p = 0.035$ ).

At present it is uncertain whether or not antidepressant monotherapy may be safer and less prone to induce affective switch in bipolar II versus bipolar I patients. Amsterdam et al. (67) and Amsterdam (68) reported two open trials of fluoxetine and venlafaxine monotherapy in bipolar II depressed patients with switch rates over short-term treatment of 3.8 and 0%, respectively. However, double-blind studies have not been conducted to affirm these preliminary observations.

Recent efforts to establish biological correlates of psychopathology and pharmacotherapy responses have suggested a possible association between antidepressant-induced mania and a functional polymorphism of the serotonin transporter gene, in which the short allelic variant for the 44 base pair promoter region of this gene may be disproportionately represented among individuals who switch from depression to mania while taking an antidepressant (69). This finding supports the view that antidepressant-induced mania could in fact be a phenotype of bipolar illness, demarcating a biologically distinct patient subgroup.

The extent to which bipolar patients with a known history of antidepressant-induced mania are at increased risk for future antidepressant-induced manias has not been systematically addressed in the literature. However, findings from at least two studies are informative in this regard. Baldassano et al. (70), treating 20 depressed bipolar patients with paroxetine (plus concomitant mood stabilizers in most instances), noted that 65% of their sample had previous antidepressant-induced manias ( $n = 13$ ). Although only one subject in this study developed hypomania while taking paroxetine, it was one of the 13 patients with a history of previous antidepressant-induced

mania. In addition, Fogelson et al. (71) observed incipient manias in six of the 11 patients treated with bupropion (54.5%), and nearly all had a previous history of manias induced by other antidepressants.

### Severity of antidepressant-induced manias

In a comparative study of 49 bipolar patients with antidepressant-induced manias and 49 matched inpatients with spontaneous manias, Stoll et al. (72) observed that antidepressant-induced manias tended to be of relatively milder severity and shorter durations when compared with spontaneous manias. Similarly, Goldberg and Whiteside (8) found that no clinical intervention was made in 26.3% of antidepressant-induced manias; the most commonly observed clinical event was elimination of the antidepressant drug (occurring in 52.6% of cases), while in an additional 15.7% a mood stabilizer was added after eliminating the antidepressant. Only in 5.2% of cases was an antidepressant continued, but with the addition of a mood stabilizer. Antidepressant-induced manias seldom led to hospitalization or functional impairment in this cohort. In addition, Boerlin et al. (6) judged antidepressant-induced manias as being severely disruptive to overall functioning in only 10% of 79 antidepressant trials, which reflected only about one-third of all antidepressant-induced manias (eight of 22 total inductions involved manias, while the remaining 14 were hypomanias). However, the authors noted that tricyclic-induced manias appeared to be more intense when compared with switches related to other antidepressant classes.

By contrast, Howland (73) described the emergence of relatively severe, psychotic manias induced by SSRIs in a series of 11 bipolar patients. Preda et al. (74), during a 14-month period, observed that 8.1 of 533 admissions to a university-based general hospital were the result of antidepressant-induced manias or psychosis. However, it is difficult to generalize about incidence rates for these outcomes in the absence of published longitudinal comparison data.

### Antidepressant subtypes

Although the phenomenon of antidepressant-induced mania was first described in connection with the use of tricyclic antidepressants (1), there remains little empirical information about the relative degree of safety against manic inductions with newer generation antidepressants, such as SSRIs, SNRIs such as venlafaxine, mirtazapine and

duloxetine, or other novel antidepressants (e.g. bupropion). Findings from clinical trials of antidepressant medications for bipolar depression that report rates of switch into mania or hypomania are summarized in Table 1.

A meta-analysis by Peet (75) found a statistically higher rate of antidepressant-induced manias in bipolar patients who took tricyclics (14 of 125, or 11.2%) versus SSRIs (nine of 242, or 3.7%), the latter showing no difference from switch rates into mania with placebo (two of 48, or 4.2%). Similarly, in a survey of postmarketing reports of adverse events, Barak et al. (76) noted a significantly lower rate of emergent mania or hypomania among 682 citalopram-treated patients (one, or 0.15%) when compared with 389 patients taking the adrenergic tetracyclic antidepressant maprotiline or mianserin (five, or 1.29%). Stoll et al. (72) observed that monoamine oxidase inhibitor (MAOI)- or bupropion-related manias had slightly lower levels of global psychopathology when compared with switches that occurred after fluoxetine or tricyclic use. Boerlin et al. (6), studying manias in the 2 month aftermath of antidepressant exposure in 79 depressive episodes among 29 bipolar I patients, found a higher switch rate among subjects treated with tricyclics or MAOIs than with fluoxetine. While Himmelhoch et al. (77) found similar switch rates in patients treated with tranlycypromine compared with imipramine (21 and 25%, respectively), the authors noted that most tranlycypromine-induced switches into hypomania occurred after an initial improvement in depressive symptoms, with evident signs of euthymia. By contrast, tricyclic-induced switches in that study more often led to mixed states than pure euphoric manias, and seldom first produced remissions from depression. This could suggest fundamental differences in the switch process between MAOIs and tricyclics, as well as the possibility that MAOI-induced manias tend to be of milder severity and morbidity. This is consistent with the findings of Stoll et al. (72) mentioned above. Little systematic prospective data exist comparing switch rates with older versus newer antidepressants added to mood stabilizers. A preliminary analysis by Post et al. (78) of double-blind data with bupropion, sertraline or venlafaxine yielded an overall switch rate into hypomania or mania of 14% during acute treatment. This rate is generally comparable with incidence rates reported with older generation antidepressants (see Table 1).

It is theoretically possible that combination antidepressant therapy could increase the vulnerability for switches in some patients, although data either to support or refute this hypothesis are

virtually absent from the literature, and limited only to case reports (79, 80). Nevertheless, the Expert Consensus Guidelines for the Treatment of Bipolar Disorder (81) advise changing antidepressant classes after an initial non-response, rather than augmenting a first antidepressant with a second, as is often the case in treatment-resistant unipolar depression.

Bupropion is described in some treatment practice guidelines (81) as having a relatively lower switch rate than other antidepressants, based largely on the double-blind comparison of bupropion with desipramine, showing comparable antidepressant efficacy but significantly fewer inductions of mania with bupropion (82). However, it is important to recognize that data in this area are not extensive. As noted earlier, Fogelson et al. (71) added bupropion to the existing treatment regimens of 11 depressed bipolar patients, 10 with previously developed manias when treated with other antidepressants (tricyclics, fluoxetine, or phenelzine). Although antidepressant efficacy was seen in the majority of subjects after 6 weeks, six of the 11 developed manias or hypomanias, despite concomitant mood stabilizer treatment for nearly all.

Paroxetine also is described (81) as having a potentially lower switch rate than other agents. As described in Table 1, switch rates in reported studies are relatively low (0–5%) (70, 83, 84). Baldassano et al. (70) observed an induction of hypomania in one of 20 depressed bipolar patients taking paroxetine plus standard mood stabilizers as well as an acceleration of cycling in a second patient.

Lifetime naturalistic data from the Cornell Bipolar cohort (8) indicate no significant differences across antidepressant classes with regard to the prevalence of antidepressant-induced manias. Across all classes studied, an overall mania induction rate of 16% was observed, ranging from as low as 10–15% with tricyclics or SSRIs to as high as 25% with venlafaxine. The only double-blind trial of the reversible inhibitor of monoamine oxidase A, moclobemide, reporting switch rates found comparable rates of manic/hypomanic induction between moclobemide and imipramine (85) (see Table 1).

#### **Do mood stabilizers protect against antidepressant-induced mania?**

Varying degrees of evidence exist either to support or refute the frequent clinical assumption that mood stabilizers as a class are effective in blocking the emergence of mania soon after beginning an

antidepressant drug. Some initial reports supported the view that lithium served as an effective prophylaxis against tricyclic-induced mania (86), although in a double-blind comparison of bupropion or desipramine (added to lithium, valproate, both in combination, or carbamazepine) for bipolar depression, manic inductions occurred in three of 10 patients taking desipramine (82). Over the course of a 1-year continuation phase, a total of five patients taking desipramine in this study had a manic episode. These included three of eight taking lithium (37.5%), one of four taking valproate alone (25.0%), one of two taking lithium plus valproate (50.0%), and none taking carbamazepine.

In a retrospective chart review, Bottlender et al. (87) found that depressed bipolar patients who took lithium or valproate were less likely to develop mania or hypomania while taking tricyclic antidepressants. However, no significant differences in manic switch rates were seen on or off mood stabilizers during antidepressant treatment with other antidepressant drug classes including SSRIs and MAOIs. Henry et al. (7) found that lithium, but not valproate, was associated with a lowered rate of manic or hypomanic switches during antidepressant pharmacotherapy. Goldberg and Whiteside (8) observed no significant differences in rates of manic or hypomanic inductions across antidepressant classes in either the presence or absence of concurrent therapy with lithium or divalproex. It is possible that poor mood stabilizer adherence could have been present yet undetected in some of the preceding naturalistic studies, although Stoner et al. (88) found that four of nine bipolar patients developed manic symptoms when an antidepressant was added to valproate, even when serum valproate levels exceeded 50 mcg/mL. No data are available from study designs involved the randomized presence or absence of a mood stabilizer during pharmacotherapy with standard antidepressants for bipolar depression.

If successive antidepressant exposures may constitute a form of behavioral sensitization, as our group previously has proposed (8), one might then expect antikingling agents to afford greater protection against antidepressant-induced manias when compared with lithium or other non-anticonvulsant mood stabilizers (e.g. atypical antipsychotics). While this hypothesis has not yet undergone direct empirical assessment, several preliminary reports fail to demonstrate a more robust protective effect with anticonvulsants such as divalproex or carbamazepine when compared with lithium in this at-risk clinical subgroup (7, 8).

### Is antidepressant-induced switching a dose-related phenomenon?

Little empirical evidence currently exists to clarify the extent to which inductions of mania during antidepressant pharmacotherapy represent a categorical phenomenon or a more dose-dependent outcome that could occur at varied points in the course of treatment. How clinicians attribute causality to the use of antidepressant drugs after the emergence of mania likely entails a number of factors. A first consideration involves discerning manias that are likely drug-induced from those which represent the natural course of the illness. No consensus exists, as yet, for establishing a maximal reasonable time frame (or likely at-risk window) for determining how long after beginning an antidepressant mania or hypomania can plausibly occur. The issue becomes further complicated by rapid cycling (where spontaneous switches are inherently more likely) and by the potential for antidepressants to accelerate cycle frequency over time (5). In the Cornell Bipolar cohort (8), manias or hypomanias deemed consequent to antidepressant use occurred a mean ( $\pm$  SD) of  $36 \pm 32$  days after antidepressant initiation. Because DSM-IV identifies 8 weeks as the time period needed to separate distinct affective episodes with regard to intermorbid recovery, this interval might represent a plausible maximum time after starting an antidepressant to attribute mood switches to pharmacotherapy rather than to the natural course of illness. This time frame for judging an adverse drug event is analogous to the customary time frame in which acute antidepressant efficacy is determined. Notably, the related (but separate) concept of cycle acceleration caused by antidepressants may represent a more chronic mechanism, one that likely extends beyond the proposed 8-week risk window for acute induction.

It is presently unknown to what extent the switch phenomenon could be dose-dependent. In their study reporting a relatively high rate of manic switches with bupropion (about 55%), Fogelson et al. (71) used a fairly high dose of study drug, leaving open the possibility that switches into mania or hypomania might have been less extensive with lower dosages, or with a less rapid dose escalation strategy. This hypothesis is consistent with the possibility that antidepressant dosage reductions might attenuate the emergence of mania or hypomania, and could reflect a dose-response relationship. Given the paucity of data on this topic, further controlled studies with larger sample sizes are needed to affirm this hypothesis.

A further question concerns the emergence of mania or hypomania in patients who had been clinically stable at a steady antidepressant dose who then demonstrate destabilization after dosing adjustments, often in the context of re-emergent depressive symptoms. While this phenomenon has been observed anecdotally by many practitioners, there is no formal literature based on randomized trials in order to establish causality – that is, differentiating the natural evolutionary course of illness from mood events unambiguously caused by treatment changes. It is possible that rapid dose escalations could play a role in triggering a manic switch process, although no formal studies yet exist comparing gradual versus slower-dose antidepressant escalation rates to test this hypothesis.

A final concern involves the safety of rechallenges with a particular antidepressant drug after observed inductions of mania. This question becomes especially difficult in patients who may show initial signs of a favorable antidepressant response but then later switch into mania, potentially after a dosage increase [as described by Himmelhoch et al. (77) in the case of MAOIs]. In the absence of systematic empirical data to guide such decisions, clinical wisdom would generally favor avoiding agents known to destabilize mood in a given patient, particularly if manic switches had been severe. After the resolution of relatively mild, transient or questionable hypomanias, rechallenges with lower antidepressant doses may prove efficacious for some patients if undertaken with caution and vigilance.

**Clinical guidelines, implications and future research directions**

Because depressive onsets constitute the majority of initial presentations of bipolar illness (36), there is a compelling need for clinicians to remain alert to the potential for polarity conversions in subgroups of initially depressed patients who have a heightened risk for bipolar illness. Use of antidepressants without mood stabilizers in such patients is especially of concern given recent findings by our group (59) that delayed mood stabilizer initiation for index lifetime *depressive* episodes may be associated with an elevated risk for lifetime suicide attempts.

A number of clinical factors can be described to minimize risks for antidepressant-induced switches, which may be summarized as follows:

- (i) Optimize mood stabilizers, particularly lithium (7).

- (ii) Use antidepressants cautiously, if at all, in patients with rapid cycling (2, 5, 21, 89) or recent manias/hypomanias (90). Consider their elimination as a possible treatment strategy for cycle acceleration (91).
- (iii) Among suboptimal antidepressant responders, consider changing antidepressant classes rather than augmenting with multiple antidepressants (7, 23, 79, 81).
- (iv) Consider a heightened risk for switches among patients with a prior history of antidepressant-induced mania (6, 71), comorbid substance abuse (8), multiple antidepressant trials (5, 8), a bipolar family history (73), and known bipolar patients who take antidepressants without mood stabilizers (7).
- (v) Bupropion and paroxetine are considered to have a lower risk than other antidepressants for precipitating mania according to expert consensus guidelines (81), although data on relative risks across antidepressant classes are not extensive.
- (vi) Use gradual rather than rapid antidepressant dose escalations.
- (vii) Observe for signs of emergent mania/diminished sleep, and consider antidepressant dosage reductions accordingly.

Similarly, strategies for managing antidepressant-induced manias may include the following:

- (i) Consider a gradual rather than abrupt cessation of antidepressants, even in the presence of hypomania, to minimize physiologic withdrawal effects that could trigger or exacerbate hypomania (23).
- (ii) Identify additional factors that can destabilize mood (e.g. alcohol or drug abuse, poor sleep hygiene) and address them clinically.
- (iii) In patients *with* a known history of bipolar I or II disorder, existing mood stabilizers should be optimized alongside the elimination of any antidepressant agents (91). Breakthrough manias that persist after antidepressant elimination and optimization of a first mood stabilizer may warrant augmentation with a second mood stabilizer or antipsychotic (81, 91).
- (iv) In patients *without* a known history of bipolar I or II disorder, appropriate management of ongoing symptoms after eliminating antidepressants would include the use of conventional or (preferably) atypical antipsychotic drugs (e.g. olanzapine) or benzodiazepines. Standard mood stabilizers may warrant introduction based on the severity,

duration, and clinical characteristics of a switch event.

- (v) In deciding when and whether to terminate a mood stabilizer in patients without a previously declared history of bipolar illness, consider the need for ongoing mood stabilizer pharmacotherapy based on risk factors for diagnostic polarity conversions (notably, early age at onset, a bipolar family history, psychosis when depressed, and hyperthymic temperamental features) (42, 47, 48, 51, 52).
- (vi) Future antidepressant trials would be advisable only if undertaken after the introduction and therapeutic dosing of a standard mood stabilizer. Rechallenges with the same agent at a reduced dose should not be attempted unless done so with caution and close monitoring.

Finally, based on the existing literature, a number of clinical and research implications can be identified that warrant further investigation. These include the following:

- (i) There is a need to achieve a consensus definition within the field as to what constitutes a switch into mania (as differentiated from activation or agitation) and to adopt an appropriate maximal time frame for reasonably attributing emergent manias or hypomanias to antidepressant use (rather than to the natural course of illness). Related to this is the need for better means to discriminate stimulation effects of antidepressants from subsyndromal manias. *We would propose a two-part operational definition of antidepressant-induced manias based on the nature and extent of clinical features. Type I switches into mania or hypomania would denote full syndromes as defined by the symptom, severity, and duration criteria described in DSM-IV; Type II switches would denote the emergence of a distinct but subthreshold period of elevated or irritable mood accompanied by at least two of the DSM-IV associated signs and symptoms of mania or hypomania, regardless of their duration. We further propose that an 8-week period be applied as the time frame after beginning an antidepressant at a specific dose in which newly emergent manias or hypomanias could be attributed with reasonable likelihood to the effects of an antidepressant.* This cut-off has been chosen because 8 weeks is the customary period over which antidepressant response is gauged. While it may be possible that medication-induced switches occur after 8 weeks, in the absence of controlled data our

experience is that this is a less commonly encountered event (8), and might entail the related longer-term concept of cycle acceleration. Manias or hypomanias that occur beyond this time frame should be considered as the likely or plausible consequence of antidepressant use only if a meaningful change in dosage preceded the switch.

- (ii) Additional research is needed to evaluate antidepressant-induced cycle acceleration as a phenomenon relevant to mood destabilization but *distinct* from acute inductions of mania. The time frame in which longitudinal cycle accelerations may result from antidepressant use (rather than to the natural course of illness) likely extends beyond the acute 8-week window proposed above for acute mania inductions, but empirical data are not yet available to validate this.
- (iii) Further clarification is needed about the extent to which antidepressant-induced manias may be dose-related phenomena, or may occur beyond the initial 8 weeks of antidepressant treatment when dosage increases occur. Randomized clinical trials are needed to discern these issues.
- (iv) Clinicians should not routinely assume the protective role of mood stabilizers for preventing antidepressant-induced manias. While their presence *may* help to reduce the risk for switching when an antidepressant is introduced – particularly in the case of lithium – their differential efficacy in this regard remains controversial and requires additional research clarification.
- (v) Conflicting data presently exist for a number of clinical characteristics as possible predictors of switch events during antidepressant use. These include the roles of gender, age at onset, bipolar I versus bipolar II subdiagnoses, and number of previous episodes. Further studies are needed to help resolve these ambiguities, as well as to affirm reports of the predictive value of variables currently *without* contradictory evidence, including the presence of a bipolar family history, number of antidepressant trials, histories of comorbid substance abuse, hyperthymic temperamental features, and a known history of antidepressant-induced mania.
- (vi) All antidepressant drugs appear to confer a heightened risk for antidepressant-induced mania in vulnerable populations. Determining which antidepressants may bear a relatively greater or lesser risk may depend in part on *patient-specific* rather than *medication-specific*

Table 3. Clinical and demographic predictors of antidepressant-induced mania

Feature	Supportive evidence	Contrary evidence
Gender	Antidepressant-induced cycle acceleration more common in women than men (6)	Comparable male:female risk for acute antidepressant-induced mania (6, 8)
Early age at onset	Younger age associated with tricyclic-induced switches (99)	No age relationship with antidepressant-induced switches (6)
Age	Citalopram (76) or tricyclic (99)-induced manias seen more often among older depressed patients	None reported
Psychosis	No data reported	No data reported
Bipolar I versus II	Antidepressant-induced cycle acceleration more frequent among bipolar II than bipolar I patients (6); MAOI-induced manias more common among bipolar I than bipolar II patients (77)	Comparable rates of antidepressant-induced mania or non-inductions with antidepressants among bipolar II patients (8) or among bipolar I versus bipolar II patients (7)
Number of past episodes	Antidepressant-induced manias associated with a greater number of past manic episodes (6)	No relationship between antidepressant-induced manias and number of past manic (5, 7) or depressive episodes (6)
Family bipolar history	Severe SSRI-induced manias among patients with a bipolar family history (73)	None reported
Substance abuse	Alcohol or other drug abuse comorbidity may increase for antidepressant-induced mania (8)	History of substance abuse was not associated with history of antidepressant-induced mania in NIMH STEP-BD cohort (9)
Multiple antidepressant trials	Antidepressant-induced manias associated with more antidepressant trials/year (5, 8, 9)	None reported
Hyperthymic temperament	Hyperthymic features associated with antidepressant-induced mania (7)	None reported
Lack of concomitant mood stabilizer	Antidepressant-induced mania more likely in the absence of lithium (7)	Switch events with antidepressants have been shown to occur with or without concurrent valproate (7, 8) or lithium (8), and even when serum valproate levels are therapeutic (87)
History of antidepressant-induced mania or hypomania	Most bipolar patients who became manic while taking bupropion had previously become manic on other antidepressants (71)	None reported
History of rapid cycling	Associated with a 1.8-fold increased risk of antidepressant-induced mania in the NIMH STEP-BD cohort (9)	None reported

risk factors. Future studies that address differential risk across antidepressant classes should ideally stratify subjects (*a priori* or else *post hoc*) on the basis of such patient-specific features as summarized in Table 3, particularly those without contradictory evidence in the literature, as described above.

- (vii) More empirical information is needed about the safety and efficacy of rechallenging with the same antidepressant agent but at a reduced dose after the resolution of a switch from depression to mania, followed by an eventual recurrent depression. Existing evidence would caution against this intervention unless it is undertaken with careful vigilance.
- (viii) Evidence-based parameters have not, as yet, been established for the safety, efficacy and dosing of antidepressant medications in contemporary bipolar patients with rapid cycling, where the risk for mood destabilization appears especially high (2, 21). In the NIMH Collaborative Study on the Psychobiology of Depression, Wehr et al. found that no

patients with rapid cycling became euthymic with mood stabilizers while taking antidepressants (89), although virtually complete remissions were obtained in over one-third of subjects when antidepressants were discontinued. However, only tricyclic antidepressants were used in this study, it is unknown whether results might differ in a population taking newer antidepressant classes. Nonetheless, practice guidelines generally caution against the use of antidepressant drugs in bipolar patients with rapid cycling except for short periods of time as needed (81, 91).

- (ix) Further basic and clinical studies are needed to better determine whether antidepressant-induced mania reflects a possible phenotype or endophenotype of bipolar illness as suggested by molecular genetic studies of candidate gene polymorphisms such as the serotonin transporter (69) in a biologically definable bipolar subgroup.
- (x) Risks for antidepressant-induced mania need to be identified in other special populations,

including children, the elderly, and the medically ill. Related to this is the need to identify risk factors in patients presenting with unipolar depression who may be at risk for subsequent conversion to a bipolar diathesis, and the possible relationship between use of antidepressant medications and this outcome.

In summary, antidepressant-induced manias are common, although often under-appreciated risks of pharmacotherapy for bipolar illness. The potential for mood *destabilization* due to antidepressant exposure can be minimized by recognizing risk factors and optimizing standard mood stabilizers – particularly lithium – in both the short- and long-term management of depression in patients with bipolar disorder.

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