Bipolar Depression and Antidepressant-Induced Mania: A Naturalistic Study

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Background: The likelihood and character of antidepressant-induced mania remain important but poorly understood factors in the treatment of bipolar depression.

Method: We examined the response to naturalistic treatment of 29 bipolar I patients who experienced a total of 79 depressive episodes. Treatment consisted primarily of mood stabilizers used alone (N = 31) or in combination with antidepressants (N = 48). Intensity of baseline mood stabilizer therapy, adequacy of added antidepressant therapy, intensity of ensuing mania or hypomania, and course of illness prior to study were measured, and selected comparisons were made between treatment groups.

Results: Postdepressive mood elevations (i.e., switches) that occurred during or up to 2 months after each depressive episode were present in 28% (22/79) and judged to be severely disruptive in only 10% (8/79) of episodes. Examining only the first episode per patient, a history of a greater number of past manic episodes was associated with a higher risk of switching ($p < .023$). Antidepressant treatment combined with mood stabilizer therapy was not associated with higher rates of postdepressive mood elevation than mood stabilizer therapy alone. At a descriptive level, subjects treated with tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) were associated with a higher switch rate than those treated with fluoxetine; TCAs were also associated with more intense switches.

Conclusion: The frequency and severity of postdepressive mood elevation associated with acute or continuation antidepressant therapy may be reduced by mood stabilizers. Such elevations may be more likely in patients with a strong history of mania.

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The continuing debate over antidepressant-induced manic episodes has long complicated the establishment of an optimal treatment paradigm for bipolar depression.[1,2] Maintenance use of antidepressants in the absence of mood stabilizers has been shown to double the rate of manic episodes when compared with placebo,[3] whereas antidepressant maintenance therapy with mood stabilizers has been less clearly associated with increasing switch rates.[4,5] In the case of briefer antidepressant use, bipolar patients taking antidepressants alone or in conjunction with mood stabilizers[6–8] have been observed to have a high rate of switching to manic states, with perhaps a particular risk in the initial several weeks of therapy.[6,7] The possible confounding factor of spontaneous switch rates, however, is highlighted in both controlled[3,5] and uncontrolled studies.[9] As noted by Coryell and colleagues in their discussion of rapid cycling, "major depression in the context of a bipolar illness may both anticipate a period of rapid cycling [or switching] and provoke treatment with antidepressants, leading to a falsely apparent causal connection between these 2 events."[10(p129)] Whether varying intensities of mood stabilizer treatment,[11] choice of antidepressant,[7,12–16] and other factors[17] affect the frequency or intensity of switching in the acute or continuation treatment of bipolar depression also remain important open questions. With these considerations in mind, we followed a group of bipolar I depressed patients receiving naturalistic treatment and examined the frequency, intensity, and timing of switches to manic or hypomanic states.

METHOD

Subjects in this study were outpatients followed in the UCLA Affective Disorders Clinic for at least 2 consecutive years between 1984 and 1990 who met DSM-III[18] criteria for bipolar disorder (and who also would meet DSM-IV criteria for bipolar I disorder) and who had experienced at least 1 major depressive episode while in the clinic. Twenty-nine subjects who experienced a total of 79 major depressive episodes while in the clinic were included in the study. Treatment was naturalistic, with follow-up visits occurring as needed from every week to every few months. On average, patients were seen on a monthly basis. At each visit, the treating psychiatrist filled

out a detailed symptom checklist covering all DSM-III mood symptoms for the period since the last clinic visit. Symptom data were checked against the narrative progress note in which pertinent laboratory results and changes in medication were also systematically documented.

Affective episodes were identified by inspection of a symptom time line for each subject constructed by research staff employing a 9-point scale for rating symptom intensity and polarity used in previous studies[19,20] with demonstrated interrater reliability (percentage exact agreement for rating symptom level = .83%) (Table 1). An episode was considered completed either at the time of hypomania or mania onset, or when followed by a return to baseline mood state for at least a month with only moderate depressive symptoms (i.e., dysthymia, minor depression by Research Diagnostic Criteria [RDC],[21] or nearly meeting DSM-III criteria for major depression), whichever came first. Any later return of more substantial depressive symptoms otherwise meeting DSM-III criteria for major depression was regarded as a separate episode. Manic or hypomanic episodes were noted if they occured during or up to 2 months following each depressive episode.

Intensity of mood stabilizer regimens at the time of onset for each study episode was rated according to a 5-point scale modeled after that developed by Keller[22] and used in 2 prior studies.[19,20] Serum lithium levels at the time of episode onset were estimated by using the most recent available level at that dose, or, when this information was not available, by extrapolating from the most recently obtained blood levels at comparable doses. Other baseline psychotropic medications were also recorded.

Depressive episodes were divided into 2 groups: (1) episodes for which ensuing treatment involved only mood stabilizer therapy (MS group) and (2) episodes in which antidepressants were used in addition to the mood stabilizers (MSA group). Added antidepressant treatment was further categorized according to medication type: tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), fluoxetine, or bupropion. Adequate antidepressant treatment was defined as 3 weeks or more at a specified minimum daily dose (nortriptyline = 75 mg; other tricyclics = 150 mg; phenelzine = 45 mg; isocarboxazid or tranylcypromine = 30 mg; fluoxetine = 20 mg; bupropion = 300 mg).

Of the 79 depressive episodes, 31 were in the MS group and 48 were in the MSA group. Fourteen subjects had only 1 study episode each, while the other 15 subjects had multiple episodes. Seven subjects had episodes in both treatment groups. Five subjects had more than 5 study episodes each, representing a total of 37 episodes, with 35 of these categorized as MSA treatment.

Baseline mood stabilizers used singly or in combination included lithium (N = 59 episodes), carbamazepine (N = 5), valproic acid (N = 6), and verapamil (N = 6). Neuroleptics were employed as baseline treatment in 12 cases. Other baseline medications included benzodiazepines, thyroid supplements, and beta blockers, which were involved in 23, 13, and 2 episodes, respectively. In 19 episodes, baseline antidepressants were already being prescribed: 17 in the MSA group, to which further antidepressant therapy was added, and 2 in the MS group, in which the baseline antidepressant therapy was left unchanged. The additional antidepressant therapy usually consisted of an increase in the dose of the baseline antidepressant or, less commonly, the use of a new antidepressant and discontinuation of the baseline antidepressant. Doses and duration of added antidepressant treatment were deemed adequate in 71% (34/48) of cases overall, with no significant difference between antidepressant groups. There were 2 episodes, both within the MSA group, that also received intra-episode adjunctive treatment with methylphenidate, sleep deprivation, trazodone, or electroconvulsive therapy.

For the 27 index depressive episodes for which complete data were available, baseline mood stabilizers consisted of lithium in 21 cases, carbamazepine in 2 cases, and verapamil in 1 case. Additional baseline medications included neuroleptics (N = 5 episodes), benzodiazepines (N = 8), thyroid supplements (N = 5), and beta blockers (N = 1). Four of the index episodes in the MSA group also involved the use of baseline antidepressants.

Owing to the descriptive nature of the study, 2-tailed tests of significance in all inferential statistics were reported because no directional predictions were made. All statistical analyses were carried out using the SYSTAT for Windows 5.0 and the SPSS/PC 4.0 (SPSS, Inc., Chicago, Ill.) statistical analysis programs. Overall, group differences on all categorical variables were evaluated using the

Table 1. Scale for Symptom Intensity and Polarity*

Rating	Description	Criteria
0	No symptoms	
1	Mild symptoms	M1: No more than 2 total symptoms for mania, including the mood symptom (DSM-III criterion A)
		D1: No more than 2 total symptoms for depression, including the mood symptom (DSM-III criterion A)
2	Moderate symptoms	M2: Diagnosable hypomania by RDC
		D2: Dysthymia, RDC minor depression, or nearly meets criteria for DSM-III major depressive episode
3	Marked symptoms	M3: Diagnosable manic episode by DSM-III criteria
		D3: Diagnosable depressive episode by DSM-III criteria
4	Severe symptoms	M4: Mania requiring hospitalization; severe dysfunction
		D4: Major depression requiring hospitalization or with serious suicide attempt

*Adapted from reference 19. Abbreviations: D = depression, M = mania, RDC = Research Diagnostic Criteria.[21]

Table 2. Demographic Variables for Index Episodes of Depression*

Variable	Treatment Group MS[a]	MSA[a]
Subjects	14	13
Age, y	43.9 ± 11.1	49.2 ± 6.8
Female, N (%)	6 (43)	8 (62)
Age at onset of bipolar disorder, y	23.3 ± 6.0	21.9 ± 6.7
Manic episodes	7.2 ± 3.7	5.4 ± 4.5
Major depressive episodes	4.3 ± 4.4	6.7 ± 3.9
Hospitalizations	5.8 ± 2.8[b]	2.2 ± 2.0[b]
Affective episodes per year	0.6 ± 0.4	0.8 ± 0.5

*Abbreviations: MS = mood stabilizer, MSA = mood stabilizer plus antidepressant.
[a]Values are mean ± SD except as noted.
[b]Subjects in the MS group had a significantly greater number of prior hospitalizations than subjects in the MSA group (t = 3.734, df = 23, p < .001).

chi-square statistic. The Yates correction for continuity was employed for 4-cell analyses in which there was an expected value of 5 or more in each cell. For continuous dependent measures, parametric tests were used.

Switch rates and switch intensities are described for all episodes. These variables are also reported separately for subjects with 5 or fewer study episodes and for subjects with more than 5 study episodes given that the latter group may have had a disproportionate effect on the data when considered in the aggregate. Unpaired t tests for independent groups were performed to assess the effects of MS group and MSA group treatments during the index episode for the 27 subjects with complete data for these episodes and to identify demographic and clinical historical variables associated with switching. For the 7 patients who received both MS and MSA treatments during the course of the study, within-subjects analyses were performed using paired t tests.

For all subjects, the mean ± SD age was 40 ± 9.4 years, and 55% of subjects were female. The mean age at onset of bipolar disorder was 22 ± 6.4 years. Prior to entering the clinic, the subjects reported having had a mean ± SD of 6.5 ± 4.0 manic episodes, 5.4 ± 4.2 major depressive episodes, and 4.2 ± 3.0 psychiatric hospitalizations, with an annual rate of 0.6 ± 0.4 affective episodes per year. In comparing similar variables for the 27 subjects with complete index episode data (see Table 2), only the number of prior hospitalizations was found to differ significantly (t = 3.734, df = 23, p = .001) between those subjects who had index episodes in the MS group (N = 5.8; 95% confidence interval = 4.2 to 7.4) versus those who had index episodes in the MSA group (N = 2.2; 95% CI = 1.0 to 3.4).

RESULTS

For all depressive episodes, switches to hypomania or mania occurred in 28% (22/79) of episodes overall, 26% (8/31) of MS episodes, and 29% (14/48) of MSA episodes (see Table 3). For the 5 subjects with more than 5 study episodes, the overall switch rate was 35% (13/37). Switch rates for the TCA, MAOI, and fluoxetine subgroups were 32% (7/22), 35% (6/17), and 12% (1/8), respectively. Only 1 study episode involved bupropion treatment, and switching did not occur after this episode. Sixty-four percent (14/22) of switches were hypomanic, while 36% (8/22) were manic. Using the symptom intensity ratings mentioned previously, the mean switch intensity equaled 2.1 ± 1.0 overall, 1.9 ± 1.2 within the MS group, and 2.3 ± 0.8 within the MSA group. Switch intensity for the TCA and MAOI subgroups averaged 2.6 ± 0.8 and 2.0 ± 0.9, respectively, with the single fluoxetine-treated switch episode having an intensity of 2.

For episodes among subjects experiencing 5 or fewer study episodes, switch rates and intensities were not found to significantly differ when compared with episodes among subjects having more than 5 study episodes each (see Table 4). Nonetheless, switch rates for the > 5 episodes/subject group were higher, often by a factor of 2 or more, when compared with the < 5 episodes/subject group.

For index depressive episodes, the overall switch rate was 19% (5/27) with corresponding values of 21% (3/14) in the MS group and 15% (2/13) in the MSA group, a nonsignificant difference. By antidepressant type, the index episode switch rate was 18% (2/11) for TCA-treated episodes and 0% (0/2) for MAOI-treated episodes; no index episodes involved fluoxetine treatment. Mean switch intensity for index episodes overall was 2.4 ± 0.9, with 40% (2/5) being hypomanic and 60% (3/5) manic. Switch intensities within the MS (2.3 ± 1.2) and MSA (2.5 ± 0.7) groups did not differ significantly. Mood stabilizer intensity ratings also did not differ significantly between the MS group (3.3 ± 1.3) and the MSA group (3.0 ± 1.2), nor between those index episodes marked by switching (3.1 ± 1.3) and those that were not (3.4 ± 0.9).

For the 7 subjects with at least 1 episode each in the MS and MSA groups, a within-subject comparison revealed a switch rate of 29% for episodes in the MS group and 33% for episodes in the MSA group, a nonsignificant difference. A similar comparison of mood stabilizer treatment intensities between MS episodes (2.47 ± 1.22) and MSA episodes (2.66 ± 1.32) revealed no significant differences. Within-subject comparison of switch intensity was precluded by the small number of subjects (N = 2) having at least 1 switch episode each in the MS and MSA groups.

The likelihood of switching within the index of bipolar disorder episodes was not associated with age, sex, or age at onset of bipolar disorder. Similarly, no association existed with the number of prior depressions, hospitalizations, or total episodes. The number of prior manic episodes, however, was associated with switching in the index episodes, with 10.0 (95% CI = 6.5 to 13.5) prior manias among patients who switched versus 5.5

Table 3. Treatment Group Outcomes: All Episodes Versus Index Episodes*

Treatment Group	All Episodes: Episodes, N	All Episodes: Switch Episodes N	All Episodes: Switch Episodes %	All Episodes: Switch Intensity[a]	Index Episodes: Episodes, N	Index Episodes: Switch Episodes N	Index Episodes: Switch Episodes %	Index Episodes: Switch Intensity[a]
All groups	79	22	28	2.1 ± 1.0	27	5	19	2.4 ± 0.9
MS group	31	8	26	1.9 ± 1.2	14	3	21	2.3 ± 1.2
MSA group	48	14	29	2.3 ± 0.8	13	2	15	2.5 ± 0.7
TCA	22	7	32	2.6 ± 0.8	11	2	18	2.5 ± 0.7
MAOI	17	6	35	2.0 ± 0.9	2	0	0	…
Fluoxetine	8	1	12	2.0	0	…	…	…
Bupropion	1	0	0	…	0	…	…	…

*Abbreviations: MAOIs = monoamine oxidase inhibitors, TCAs = tricyclic antidepressants. Symbol: … = not applicable.
[a]Nine-point scale (see text) for rating intensity and polarity with values of 0 to + 4 for euthymia to severe mania expressed as mean ± SD.

Table 4. Comparison of Subjects Who Had 5 or Fewer Depressive Episodes With Subjects Who Had More Than 5 Depressive Episodes

Treatment Group	≤ 5 Episodes/Per Subject: Episodes, N	≤ 5 Episodes/Per Subject: Switch Episodes N	≤ 5 Episodes/Per Subject: Switch Episodes %	≤ 5 Episodes/Per Subject: Switch Intensity[a]	> 5 Episodes Per Subject: Episodes, N	> 5 Episodes Per Subject: Switch Episodes N	> 5 Episodes Per Subject: Switch Episodes %	> 5 Episodes Per Subject: Switch Intensity[a]
All Groups	42	9	21	2.1 ± 1.2	37	13	35	2.2 ± 0.9
MS Group	29	7	24	2.0 ± 1.3	2	1	50	1.0
MSA Group	13	2	15	2.5 ± 0.7	35	12	34	2.3 ± 0.9
TCA	11	2	18	2.5 ± 0.7	11	5	45	2.6 ± 0.9
MAOI	2	0	0	…	15	6	40	2.0 ± 0.9
Fluoxetine	0	…	…	…	8	1	12	2.0
Bupropion	0	…	…	…	1	0	0	…

[a]Nine-point scale (see text) for rating intensity and polarity with values of 0 to + 4 for euthymia to severe mania expressed as mean ± SD.

(95% CI = 3.8 to 7.2) prior manic episodes among those patients who did not switch (t = 2.440, df = 23, p < .023).

DISCUSSION

Overall, our study revealed that among depressed bipolar patients who received comparable degrees of mood stabilizer therapy under naturalistic conditions, switches occurred in roughly one quarter of episodes, with an average intensity of a low-grade mania. Examining either all depressive episodes or only index episodes, the use of additional antidepressants was not associated with more frequent or severe postdepressive mood elevations. The only predictor of switching was a greater number of past manic episodes. Depressive episodes treated with TCAs or MAOIs were more frequently marked by switching than those treated with fluoxetine, with TCA-induced switches being the most intense, although these findings did not reach statistical significance.

As with many naturalistic studies, our results are limited by a variety of methodological constraints. Most important among these is the nonrandom nature of treatment assignment. Descriptive data derived from all episodes are compromised by the sample being dominated by a few patients (i.e., 5 patients accounted for 35 episodes) whose confounding role may have been obscured by the limited power of the study. Further limitations include the sporadic use of other antidepressant treatments (e.g., stimulants) in a number of episodes, the use of baseline antidepressants, the failure to account for serum lithium levels around the time of switching, and the lack of exclusion criteria for substance abuse or other medical illnesses. Lastly, a variety of likely selection biases, such as the tendency for clinicians to avoid antidepressant therapy in patients who are perceived to be at higher risk for antidepressant-induced mania, further detract from our findings.

Several attempts were made to overcome study limitations, including the use of anchored scales for classifying degrees of mania and depression as well as for rating antidepressant and mood stabilizer treatment intensities. Index episode and within-subject analyses, although they decrease the sample size and increase the possibility of a type II error, better control for individual differences between subjects and the lack of independence between episodes within a subject. Furthermore, given the potentially important distinctions between depressive subtypes, a homogeneous diagnostic population (bipolar I patients only) of known illness severity (averaging 0.6 ± 0.4 episodes/year prior to study entry) was utilized; this degree of illness compares reasonably to findings from a cohort (N = 160) of the National Institute of Mental Health (NIMH) Collaborative Depression Study reported on by

Winokur et al.,[23] in which the annual episode rate was 0.6 ± 0.6 episodes/year.

Previous studies have cited overall switch rates ranging from 6.5%[17] to almost 95%,[24] depending on length of follow-up, proportion of bipolar I versus bipolar II versus rapid-cycling patients, duration and degree of antidepressant or concurrent mood stabilizer therapy, and inclusion of hypomanic as well as manic switches. In our study, the switch rate for antidepressant-treated index episodes was 15%. By comparison, Himmelhoch et al.[7] found a 38% switch rate for bipolar-I patients treated over a 16-week period with antidepressants (but without mood stabilizers), while Altshuler et al.[8] estimated a 35% rate of antidepressant-induced switching in their retrospective study in which mood stabilizers were variably employed.

The relatively lower switch rates noted in our study and the lack of any effect of antidepressant treatment in increasing this rate may reflect the role of mood stabilizers acting as a safeguard against antidepressant-induced switching. Earlier work by Jann et al.[11] found a significant correlation between low serum lithium levels and switching that occurred during antidepressant treatment. Perhaps the most robust indicator in our study of the protective role of mood stabilizers comes from the within-subject analysis, which verified the similarity in switch rates between the MS (29%) and MSA (33%) groups while also controlling for individual differences between subjects. In a recent review of long-term, placebo-controlled antidepressant trials involving bipolar patients, Rouillon et al.[25] noted switch rates to hypomania or mania—21% (3/13) of patients receiving placebo, 51% (25/49) receiving imipramine, 21% (13/60) receiving lithium, and 28% (10/36) receiving imipramine plus lithium—that suggest a 2-fold increased risk of switching with imipramine monotherapy compared with the natural rate, with this increase ablated almost in full by the additional use of lithium.

Among individual antidepressants, the switch rates for the TCA or MAOI subgroups were approximately 3 times as high as for the fluoxetine subgroup. By comparison, in a randomized, prospective study comparing fluoxetine, imipramine, and placebo among bipolar-I depressed patients (N = 89), Cohn et al.[26] found a higher response rate among fluoxetine-treated patients without significant differences in switch rates. Twice as many patients, however, received concurrent lithium in the fluoxetine group as in the imipramine group, and among those patients treated with imipramine, over one third were given doses of 125 mg or less. Additionally, in examining bipolar depression, Peet[15] found a statistically significant ($p < .01$) lowering of switch rate to mania when paroxetine or sertraline was used (3.7%) as compared with TCAs (11.2%) but not placebo (4.2%). The lack of information regarding the use of mood stabilizers, inclusion of bipolar I versus bipolar II subjects, and absence of strict diagnostic criteria for mania, however, hamper any clear interpretation of these findings.

It is noteworthy that the switches that occurred in our study were generally of moderate intensity, were comparable across the MS and MSA groups, and were judged to be severely disruptive in only 10.1% (8/79) of depressive episodes overall. Stoll and colleagues[27] have suggested in their retrospective study that antidepressant-associated mania may be less severe than spontaneous mania and that selective serotonin reuptake inhibitors (SSRIs) or TCAs may induce manic episodes of greater severity than those induced by MAOIs or bupropion. In the study by Himmelhoch et al.,[7] imipramine was associated with manic episodes of greater intensity than those associated with tranylcypromine. On a descriptive level, our results are consistent with these observations that TCAs induce switches of somewhat greater severity than those induced by MAOIs or fluoxetine, with overall switch intensity remaining relatively modest in the context of concurrent mood stabilizer therapy.

With regard to risk factors, subjects with a greater number of prior manic episodes were more switch prone. Sachs and coworkers[14] found a similar association in their study, albeit involving subjects whose prior manic episodes occurred in the context of antidepressant treatment, while the study by Altshuler and colleagues[8] failed to identify any similar risk. Though not identified in our study, younger age and female sex have been cited in other investigations as additional risk factors for antidepressant-induced mania.

In conclusion, our study demonstrated that among a group of depressed bipolar I patients receiving naturalistic treatment including consistent use of mood stabilizer therapy, switches occurred in approximately one quarter of episodes with an average intensity of low-grade mania. Antidepressant use was not associated with either a greater frequency or intensity of such postdepressive mood elevations. At a descriptive level, switching occurred less frequently with fluoxetine than with the other antidepressants used and was less severe when MAOIs or fluoxetine were employed rather than TCAs, although additional studies are needed to confirm both of these points. The likelihood of switching was greater for patients who suffered manic episodes more frequently in the past. A more definitive understanding of these observations must await subsequent investigations that include larger numbers of subjects and that employ randomized, prospective designs.

Drug names: bupropion (Wellbutrin), carbamazepine (Tegretol), fluoxetine (Prozac), imipramine (Tofranil and others), isocarboxazid (Marplan), methylphenidate (Ritalin), nortriptyline (Pamelor and others), paroxetine (Paxil), phenelzine (Nardil), sertraline (Zoloft), tranylcypromine (Parnate), trazodone (Desyrel and others), valproic acid (Depakene and others), verapamil (Calan and others).

REFERENCES

1. Zornberg GZ, Pope HG Jr. Treatment of depression in bipolar disorder: new directions for research. J Clin Psychopharmacol 1993;13:397–408

2. Wehr TA, Goodwin FK. Can antidepressants cause mania and worsen the course of affective illness? Am J Psychiatry 1987;144:1403–1411
3. Prien RF, Klett CJ, Caffey EMJ. Lithium carbonate and imipramine in prevention of affective episodes: a comparison in recurrent affective illness. Arch Gen Psychiatry 1973;29:420–425
4. Prien RF, Kupfer DJ, Mansky PA, et al. Drug therapy in the prevention of recurrences in unipolar and bipolar affective disorders: report of the NIMH Collaborative Study group comparing lithium carbonate, imipramine, and a lithium carbonate–imipramine combination. Arch Gen Psychiatry 1984; 41:1096–1104
5. Quitkin FM, Kane J, Rifkin A, et al. Prophylactic lithium carbonate with and without imipramine for bipolar I patients: a double-blind study. Arch Gen Psychiatry 1981;38:902–907
6. Wehr TA, Goodwin FK. Rapid cycling between mania and depression caused by maintenance tricyclics. Psychopharmacol Bull 1979;15:17–19
7. Himmelhoch JM, Thase ME, Mallinger AG, et al. Tranylcypromine versus imipramine in anergic bipolar depression. Am J Psychiatry 1991;148: 910–916
8. Altshuler LL, Post RM, Leverich GS, et al. Antidepressant-induced mania and cycle acceleration: a controversy revisited. Am J Psychiatry 1995;152: 1130–1138
9. Lewis JL, Winokur G. The induction of mania: a natural history study with controls. Arch Gen Psychiatry 1982;39:303–306
10. Coryell W, Endicott J, Keller M. Rapid cycling affective disorder: demographics, diagnosis, family history and course. Arch Gen Psychiatry 1992; 49:126–131
11. Jann MW, Bitar AJ, Rao A. Lithium prophylaxis of tricyclic-antidepressant-induced mania in bipolar patients. Am J Psychiatry 1982;139:683–684
12. Benfield P, Hell RC, Lewis SP. Fluoxetine: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in depressive illness. Drugs 1986;32:481–508
13. Fogelson DL, Bystritsky A, Pasnau R. Bupropion in the treatment of bipolar disorders: the same old story? J Clin Psychiatry 1992;53:443–446
14. Sachs GS, Lafer B, Stoll AL, et al. A double-blind trial of bupropion versus desipramine for bipolar depression. J Clin Psychiatry 1994;55:391–393
15. Peet M. Induction of mania with selective serotonin re-uptake inhibitors and tricyclic antidepressants. Br J Psychiatry 1994;164:549–550
16. Prien RF, Rush AJ. NIMH workshop report on the treatment of bipolar disorder. Biol Psychiatry 1996;40:215–220
17. Nasrallah HA, Lyskowski J, Schroeder D. TCA-Induced mania: differences between switchers and nonswitchers. Biol Psychiatry 1982;17:271–274
18. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Third Edition. Washington, DC: American Psychiatric Association; 1980
19. Ellicott A, Hammen C, Gitlin M, et al. Life events and the course of bipolar disorder. Am J Psychiatry 1990;147:1194–1198
20. Gitlin MJ, Swendsen J, Heller TL, et al. Relapse and impairment in bipolar disorder. Am J Psychiatry 1995;152:1635–1640
21. Spitzer RL, Endicott J, Robins E. Research Diagnostic Criteria: rationale and reliability. Arch Gen Psychiatry 1978;35:773–782
22. Keller MB. Undertreatment of major depression. Psychopharmacol Bull 1988;24:75–80
23. Winokur G, Coryell W, Keller M, et al. A prospective follow-up of patients with bipolar and primary unipolar affective disorder. Arch Gen Psychiatry 1993;50:457–465
24. Wehr TA, Goodwin FK. Rapid cycling in manic-depressives induced by tricyclic antidepressants. Arch Gen Psychiatry 1979;36:555–559
25. Rouillon F, Lejoyeux M, Filteau MJ. Unwanted effects of long term treatment. In: Montgomery SA, Rouillon FA, ed. Long Term Treatment of Depression. New York, NY: John Wiley & Sons; 1992:81–111
26. Cohn JB, Collins G, Ashbrook E, et al. A comparison of fluoxetine, imipramine, and placebo in patients with bipolar depressive disorder. Int Clin Psychopharmacol 1989;4:313–322
27. Stoll AL, Mayer PV, Kolbrener M, et al. Antidepressant-associated mania: a controlled comparison with spontaneous mania. Am J Psychiatry 1994; 151:1642–1645