Indicators of Mania in Depressed Outpatients: A Retrospective Analysis of Data From the Kansas 1500 Study

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Objective: Previous prospective studies have shown that unipolar depressed patients often switch to a manic episode. Some of these studies have reported that the conversion to bipolar disorder is predicted by an early onset of depression, a positive family history for mania, and psychotic symptoms. The present study examines the strength of the relationship between these 3 indicators, both alone and in combination, and the presence of mania in a large retrospective analysis.

Method: 1458 consecutive admissions to a large, Midwestern university outpatient clinic between 1981 and 1986 were interviewed, and 1002 patients met DSM-III inclusive criteria for major depressive disorder. Of these, information about age at onset of depression, family history of mania, and psychotic symptoms was available on 744 outpatients. Two structured interviews were used to assess the 3 indicators.

Results: In this large depressed outpatient sample, the incidence of lifetime mania was 27%. Each of the 3 indicators was significantly associated with the report of mania ($p < .0001$ for all 3 indicators). The rates of mania increased as the number of indicators increased. Psychotic symptoms were the strongest indicator, followed by a family history of mania and an early age at onset of depression.

Conclusion: Depressed patients with 1 or more of these 3 indicators should be monitored for the presence of bipolar disorder. Patients with 2 or more of these indicators are especially at risk to develop mania.

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Unipolar depression that switches to mania or hypomania can present a challenge to the patient, the patient's family, and the treating clinician. The treatment of the "misdiagnosed" depression can result in painful and sometimes devastating effects. Because the switch to mania is relatively common, it would be especially useful to have a list of indicators for the potential switch to mania in depressed patients that might serve as "red flags" or warning signs to clinicians that is so far not available in DSM-IV-TR.[1] Some of the follow-up studies of depressed patients[2–15] have identified 1 or more clinical features that predicted a switch to mania.

Included among the clinical features associated with a switch to mania are an early age at onset of depression (prior to age 25 years), a positive family history of bipolar disorder among first-degree relatives, and the presence of psychotic symptoms. Less commonly identified indicators include postpartum depression, antidepressant-induced hypomania, hypersomnia with psychomotor retardation, multiple episodes of depression prior to the onset of mania, multiple hospital admissions, marked self-reproach, and guilt.[7,9]

Most of the long-term follow-up studies of depressed patients are relatively small in sample size. Because they vary so much in design and the application of diagnostic criteria, these studies often identify different clinical features associated with switching. The predictive value of

combining the most promising clinical features to evaluate their usefulness as independent indicators of bipolar disorder has not been well studied. The most frequently noted clinical features associated with the switch to mania are an early onset of depression before or at age 25 years, a positive history for mania among first-degree relatives, and the presence of psychotic symptoms. The primary objective of this retrospective study was to examine the strength of the association of these indicators, alone and in combination, with the report of mania in a sample of depressed outpatients.

METHOD

Procedure and Instruments

Over a 5-year period between 1981 and 1986, the Kansas 1500 study included all new admissions (N = 1458) to the outpatient psychiatry service of a large Midwestern teaching hospital who were interviewed. Before seeing the clinic psychiatrist, the 1458 patients were administered a structured Psychiatric Diagnostic Interview[16] (PDI) and a Psychosocial Interview Questionnaire (unpublished; available from the authors upon request) that included a psychiatric family history module.

The PDI is a structured, criterion-referenced instrument based upon the descriptive, syndromatic model of DSM-III psychiatric diagnosis. Representing an elaboration and refinement of the diagnostic system proposed by Feighner et al.,[17] the version administered to these patients in the early and mid 1980s was modified for compatibility with DSM-III criteria.[18] The face-to-face interview was developed to determine whether an individual is currently, or has ever, met diagnostic criteria for any of 15 major psychiatric disorders including major depression, mania, schizophrenia (psychosis), alcoholism, drug abuse, and others. Extensive tests of the instrument's reliability and validity can be found in its manual[16] and elsewhere.[19,20] The PDI can be administered reliably in 45 to 90 minutes by trained interviewers. Interviewers were clinic staff and individually trained and supervised third-year medical students. The PDI and all other instruments were part of the routine clinic intake procedures covered in the consent to treatment form of the psychiatric outpatient clinic of the University of Kansas Medical Center. The age at onset was determined for each positive psychiatric syndrome. The Psychosocial Interview Questionnaire obtained a social and treatment history, as well as a history of psychiatric illness among first-degree relatives. Time constraints in the clinic prevented some outpatients from completing this instrument.

Definition of Terms

Family history of mania. Family history of mania among all first-degree relatives was obtained from the subject using the Psychosocial Interview and was recorded as "yes" or "no."

Age at onset. Age at onset of depression was obtained from the PDI and ranged from childhood to old age. Twenty-one percent of this depressed sample were younger than 25 years, the cutoff age for early versus late onset of depression, at the time of the interview. Among the patients with a first depression before the age of 25 years and who also satisfied criteria for mania and had onset information (N = 144), 79% reported the depression occurring before or at the time of the first mania, and 21% reported the depression occurring for the first time after the onset of mania.

Psychotic symptoms. Any indications of psychotic symptoms, even for short periods of time, were obtained from the screening questions of the PDI and were counted as positive independent of the symptoms' association with mania or depression.

Mania. Mania was a lifetime diagnosis based upon inclusive DSM-III criteria obtained from the PDI. The prevalence of mania was 27% among the outpatients who satisfied DSM-III criteria for major depression. Hypomania was not identified.

Subjects

Of the 1458 patients administered the PDI, 1002 or 69% fulfilled DSM-III inclusive diagnostic criteria for 1 or more major depressive episodes during their lifetime. Of these 1002, 744 (74%) depressed subjects had information available about all 3 indicators for mania that were the focus of the present investigation. Socio-demographic characteristics of the final 744 were almost identical with those who were excluded because of missing data. Mean (± SD) age of the final sample was 37.5 (± 13.65) years; 67% were female; 80% were white, 14% African American, and the remaining 6% were of other racial heritage. Forty-one percent were married, 27% had never been married, 29% were separated or divorced, and 3% were widowed. In the final sample of depressed outpatients, 18% were high school dropouts, 26% completed high school or a GED, 35% attended college or technical school, and 20% had obtained college degrees. Half the sample (51%) reported being unemployed during the month before the interview, while the other 49% reported having full- or part-time jobs. The patients were employed a mean (± SD) of 2.85 (± 2.70) months during the 6 months prior to study intake.

Although the depressed subjects who were positive for mania were significantly younger than depressed subjects without mania (34.6 years vs. 38.5 years; $p < .01$), the 2 groups did not differ according to marital status, race, or education.

Statistical Analysis

Chi-square tests were performed to analyze the association between mania and each indicator separately. Relative

Table 1. Association of Each of 3 Specific Indicators With Mania in Depressed Outpatients (N = 744)

	Mania (N = 200)		No Mania (N = 544)				95% Confidence
Indicator	N	%	N	%	p Value[a]	Relative Risk	Interval
Age at onset of depression							
Early (< 25 y) (N = 445)	147	33	298	67	< .0001	1.83	1.41 to 2.46
Late (≥ 25 y) (N = 299)	53	18	246	82			
Family history of mania							
Yes (N = 155)	69	45	86	55	< .0001	2.05	1.58 to 2.52
No (N = 589)	131	22	458	78			
Psychotic symptoms							
Yes (N = 165)	80	48	85	52	< .0001	2.33	1.87 to 2.92
No (N = 579)	120	21	459	79			

[a]p Values are based on the χ^2 test.

risk ratios were also calculated for each indicator. Logistic regression analysis was performed to model the contribution and relative strength of each indicator for mania when all 3 variables are considered simultaneously. All statistical analyses were completed using the SAS Software System, version 8.1 (SAS Institute Inc., Carey, N.C.).

RESULTS

Specific Indicators

Table 1 shows the relationship between each of the 3 indicators and the occurrence of mania. The presence of each indicator for mania essentially doubles the prevalence of mania compared with the absence of the indicator. For example, patients with early onset of depression (< 25 years) were 1.83 times more likely to report mania than patients with late-onset major depression (25 years or older). Patients with a positive family history of mania in first-degree relatives were twice as likely to have mania as those patients without a family history of mania. Depressed patients who reported any psychotic symptoms, regardless of duration, were 2.33 times more likely to report mania than those who reported no psychotic symptoms. A separate analysis (not shown) revealed that these results were identical in both male and female depressed outpatients.

Number of Indicators

Table 2 shows the relationship between the number of indicators and the occurrence of mania. The prevalence of mania progressively increases as the number of indicators increases.

When none of the indicators were present, the prevalence of mania was 15%. If 1 indicator was present, the prevalence of mania was 19%. In contrast, mania occurred in 49% of those patients with 2 indicators and in 67% if all 3 indicators were present ($p < .0001$).

Combining Indicators

Table 3 shows the effect of the 3 indicators alone and in combination on the occurrence of mania. Compared with no indicator, any of the 3 single indicators raised the prevalence of mania between 4% and 7%. The occurrence of mania doubled when 2 indicators were present. Although the differences among the 3 pairs of indicators were not remarkable, the presence of psychotic symptoms with positive family history of mania appeared to have the largest impact on the occurrence of mania. As shown previously, the combination of all 3 indicators produced the largest effect, i.e., 12 percentage points higher than that of the strongest pair.

Logistic Regression

Logistic regression analysis was performed with mania as the outcome variable. The 3 indicator variables (age at onset of depression; family history of mania in first-degree relatives; and presence of psychotic symptoms) were used as predictor variables. A test of this model was significant (likelihood $\chi^2 = 84.13$, df = 3; $p < .0001$), suggesting that the 3 indicators together reliably distinguished subjects with mania from subjects without mania. Seventy percent of the subjects with mania were correctly classified.

Table 4 shows that all 3 indicators significantly contributed to the prediction of mania when the correlation among them was statistically controlled. Odds ratios and confidence intervals indicate that the presence of psychotic symptoms had a slightly stronger association with mania than the age at onset of depression or the family history variables, but these 2 also showed a reliable association. Further modeling (not shown) using combinations of variables revealed no appreciable gain in model fit statistics (AIC intercept, likelihood χ^2, Wald statistic) or in the percent correctly categorized. However, the larger model did support the conclusion (Table 3) that having all 3 indicators showed a greater association with mania than having only 2 indicators and that 2 indicators showed a greater association with mania than having only 1 indicator.

DISCUSSION

This study found that in a large sample of depressed outpatients, the incidence of lifetime mania was 27%, and

Table 2. Relationship Between Number of Indicators and Mania in Depressed Outpatients (N = 744)[a]

No. of Indicators Present	Total N	Mania Positive N	Mania Positive %
0	217	32	14.7
1	322	62	19.3
2	172	84	48.8
3	33	22	66.7

[a]$\chi^2 = 94.54$; df = 3; $p < .0001$.

Table 3. Distribution of the 3 Indicators for Mania in Depressed Outpatients (N = 744)

Indicators	N	Patients With Mania in Each Group N	Patients With Mania in Each Group %
No indicator present	217	32	15
Age at onset of depression < 25 years	251	47	19
Positive family history of mania	35	7	20
Presence of psychotic symptoms	36	8	22
Early onset + positive family history	76	34	45
Early onset + psychotic symptoms	85	44	52
Positive family history + psychotic symptoms	11	6	55
Early onset + psychotic symptoms + family history	33	22	67
Total	744	200	

3 clinical features were significantly associated with the report of a manic episode: early onset of depression before age 25, family history of mania in first-degree relatives, and the presence of psychotic symptoms. In separate analyses, the relationship between these 3 indicators and the presence of mania was equally strong for both male and female depressed outpatients.

Previous long-term follow-up studies of depressed patients have identified various clinical features that were more common in switchers to mania than in nonswitchers. The present investigation is focused on the most promising features of those follow-up studies.

With respect to earlier age at onset, this study found that 33% of patients with an early onset of depression (< 25 years) reported mania compared with 18% with late-onset depression. Akiskal et al.[7] reported that 71% of switchers to mania or hypomania had an onset of depression before the age of 25 as compared with 32% of nonswitchers. Similarly, Coryell et al.[13] found that switchers to mania and hypomania had an average age at onset of depression of 25 years, while the average onset age of nonswitchers was 31 years.

With respect to a family history of mania, in our study 155 depressed outpatients reported a positive family history of mania in first-degree relatives compared with 589 that did not. Of the group who had a positive family history (N = 155), 45% fulfilled DSM-III inclusion criteria for mania versus 22% of the group without a known family history. The relationship between a positive family history of mania and the development of mania was observed in 4 out of the 5 follow-up studies: Fifty percent of the switchers in Strober and Carlson's study[6] had a positive family history of mania; the nonswitchers had 10%. In Akiskal and colleagues' study[7] 56% of the switchers reported mania in their first degree relatives versus 2% reported by the nonswitchers. The corresponding percentages in the Coryell et al. study[13] were 19% versus 4%. Geller et al.[11] reported that a positive family history of mania in first-degree relatives was 5.8 times more frequent in switchers than in nonswitchers. Only 1 study by Goldberg et al.[15] found that a family history of mania was not significantly associated with the switch to mania in depressed patients.

Table 4. Logistic Regression Modeling the Relative Strength of the 3 Indicators for Mania

Variable	Parameter Estimate	χ^2*	Odds Ratio	95% Confidence Interval for Odds Ratios
Age at onset of depression[a]	0.66	11.96†	1.93	1.33 to 2.83
Family history of mania[b]	0.94	22.35†	2.56	1.73 to 3.77
Psychotic symptoms[c]	1.19	38.10†	3.28	2.25 to 4.79

[a]< 25 y vs. ≥ 25 y.
[b]Yes vs. no (first-degree relatives).
[c]Yes vs. no.
*Full model likelihood ratio $\chi^2 = 84.13$, df = 3, $p < .0001$.
†$p < .0001$.

The presence of psychotic symptoms was the strongest indicator for mania in this study. In our sample, 165 had psychotic symptoms, 579 did not. Patients with psychotic symptoms satisfied inclusive DSM-III diagnostic criteria for mania in 48% of the cases, compared with 21% of the depressed outpatients without psychotic symptoms. All 4 of the reviewed studies that considered psychotic symptoms reported a significant increase of psychosis in switchers compared with nonswitchers. In Strober and Carlson's study,[6] 75% of the teenagers who switched to mania had psychotic symptoms as compared with 6% of the nonswitchers. Eighty percent of Goldberg and colleagues' patients who switched to mania had psychotic symptoms as compared with 20% of nonswitchers.[15] Akiskal and colleagues' switchers to mania reported psychotic symptoms in 42% of the cases versus 15% of the nonswitchers.[7] Coryell and colleagues' switchers to mania were psychotic in 26% of the cases versus 10% in the nonswitchers.[13] Our findings reaffirm that the presence of psychotic symptoms in depressed patients is an especially reliable indicator for mania.

A major purpose of this study was to determine whether each of the 3 clinical indicators independently contributed to the report of a manic episode. The logistic regression analysis showed that each of the 3 clinical indicators was a significant contributor to the presence of

mania. Moreover, combining these independent features proportionally increased the occurrence of mania from 15% for no indicators present to 67% when all 3 clinical features were present. This study is original because it assesses the relative power of each of these 3 clinical features alone and in combination. The presence of 1 indicator would suggest a "low index of suspicion," the presence of any 2 positive features could suggest a "medium index of suspicion," and having all 3 present would suggest a "high index of suspicion" for mania.

The inclusion of these risk factors for mania in the forthcoming DSM-V under "Associated Features of Mania" could provide a valuable diagnostic aid for mental health providers. However, it must be emphasized that this is a retrospective study and certain distortions can occur when individuals in distress are asked to recall symptoms and histories in a clinic setting. A large prospective study of unipolar depressed patients in treatment is needed to confirm our findings, especially the summative effect of indicators as they accumulate in the history of a single individual over time. Until that is done, clinicians should be alert to the possible implications of age at depression onset, family history of mania, and the presence of any psychotic symptoms in the unipolar depressed patient. Two or 3 of these features should warn the clinician to watch closely for mania over the course of treatment.

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