ORIGINAL ARTICLE

Rapid Switching of Mood in Families With Multiple Cases of Bipolar Disorder

Dean F. MacKinnon, MD; Peter P. Zandi, PhD; Elliot Gershon, MD; John I. Nurnberger, Jr, MD, PhD; Theodore Reich, MD; J. Raymond DePaulo, MD

Background: Heterogeneity within the diagnostic construct of bipolar disorder is most likely an obstacle to discovering its causes. Phenomena in the bipolar spectrum, including rapid cycling, cyclothymia, and affective instability of borderline personality, may be important markers of etiologic heterogeneity. Rapid switching of mood may be central to these phenomena.

Methods: We performed a case-control study, using diagnostic data from a multisite bipolar disorder linkage study, to explore clinical and demographic factors potentially related to rapid switching in bipolar disorder. Participants were 18 years or older and members of a family in which 2 or more first-degree relatives had bipolar disorder. Of 718 individuals interviewed and diagnosed as having bipolar disorder, 603 gave sufficient information about rapid switching and thus constituted the study group (60% female; mean age, 41 years; and mean education level, 13.8 years).

Results: Rapid switching of mood was reported by 44% of interviewees and was associated with early age at onset of bipolar disorder, higher risk of anxiety and substance abuse or dependence comorbidity, suicide attempts, antidepressant drug use, and having a relative with rapid switching.

Conclusions: Rapid switching is associated with a complex clinical course of bipolar disorder. These results extend previous associations among rapid switching, anxiety, substance abuse, and early onset of bipolar disorder to a family study population. Rapid switching of mood seems to be the core phenomenon behind several variants of non–*DSM-IV* rapid cycling, *DSM-III-R* mixed states, and borderline personality disorder and the link connecting comorbidity, suicide, and early onset of bipolar disorder. Further biological investigation of the rapid-switching phenomenon is justified on epidemiologic grounds.

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From the Department of Psychiatry and Behavioral Sciences (Drs MacKinnon and DePaulo) and the Bloomberg School of Public Health (Dr Zandi), The Johns Hopkins University School of Medicine, Baltimore, Md; the Department of Psychiatry, University of Chicago, Chicago, Ill (Dr Gershon); the Institute of Psychiatric Research, Department of Psychiatry, Indiana University School of Medicine, Indianapolis (Dr Nurnberger); and the Department of Psychiatry, Washington University, St Louis, Mo (Dr Reich).

CLEAR DEFINITION of the boundaries around and the heterogeneity within the bipolar disorder diagnosis is a practical problem for clinicians and researchers alike.[1,2] Moreover, within the diagnostic category of bipolar disorder there may exist dimensions that have etiologic salience.[3] One such dimension is the rapidity of change between manias and depressions.

Rapid-cycling bipolar disorder, as defined by the *DSM-IV*, is at least 4 discrete episodes of mania or depression in a single year demarcated by clear periods of remission or by switches to episodes of opposite polarity. Thus defined, rapid cycling is believed to be an uncommon,[4,5] transient form of bipolar disorder,[6,7] which complicates management[8] and prevention[9] of episodes. There is little consistency in the literature on rapid cycling beyond these facts.[10] For example, the proportion of affected females reported in studies of rapid cycling ranges from one-fourth to three-fourths,[11] and acceleration of switching by antidepressant drug therapy has been reported across a similarly wide range.[12,13] The basis of these inconsistent findings may be the absence of a unified core concept of the phenomenon of rapid cycling: Is it an accelerated frequency of episodes, rapid polarity switching, or both?

Using only the *DSM-IV* definition of rapid cycling, one cannot adequately respond to this question, as the *DSM-IV* omits mood fluctuation at the extreme end of rapidity, that is, when episodes do not meet duration criteria for a manic or depressive episode. Episode frequency at this end of the spectrum was called "Bipolar Disorder, Mixed" in *DSM-III-R*. Rapid switching of affective state (ie, "affective lability") is found in the *DSM-IV* under the category of borderline personality disor-

der (if anywhere), and its appearance there underscores the putative connection between borderline personality disorder and affective disorder.[14-16] Empirical support for the view that rapid switching of affective state is a form of adult bipolar disorder is drawn from numerous case reports and studies of small groups.[14-17] Since the *DSM-IV* changed the criteria for mixed states and introduced a narrow definition of rapid cycling, investigators of very fast switching have had to introduce terms such as "ultra-rapid," "ultradian," and "ultra-ultra rapid" cycling into the literature.[17] The common, core element of these phenomena is the rapid switching of affective state over the course of a few weeks, days, or even hours.

A source of the difficulty in validating the rapid switching phenomenon as an expression of bipolar disorder is the apparent emergence of this form of bipolar disorder as a relatively new problem in psychiatric practice. It has been posited that rapid-switching forms of bipolar disorder barely existed in decades past,[18] with the implication that an increase in the incidence of such patterns is a result of secular trends in diagnostic practices (such as seeing mood instability as diagnostic of a bipolar spectrum disorder rather than borderline personality disorder[2]), the increasing use of antidepressant drugs,[13] the advent of lithium carbonate therapy (which triggers hypothyroidism, which may trigger rapid cycling[19]), or the increasing prevalence of stimulating drugs of abuse such as cocaine.[20]

On the other hand, there is evidence that research on rapid-switching forms of bipolar disorder may yield insight into the biological mechanisms of the illness. A low-activity allele of catecholamine-*O*-methyltransferase has been associated with rapid- and ultra-rapid–cycling bipolar disorder (but not the common form) in several[21-23] but not all[24,25] studies. A true association of very fast cycling with low-activity catecholamine-*O*-methyltransferase would potentially explain the relationship between elevated catecholamine levels and mood switching in bipolar disorder.[26,27] Thus, whether these particular biological connections prove valid, they illustrate how focusing on the rapid switching phenomenon itself may point directly to biological mechanisms behind affective disorders.

This analysis uses data on rapid switching from the diagnostic data set generated for a multisite bipolar disorder linkage study.[28,29] In this family-based case-control study, controls were individuals who had bipolar disorder without rapid switching and cases were individuals with bipolar disorder and self-reported rapid switching. Given the relative absence of previous data on the clinical and demographic correlates of rapid switching in a population of this kind, our aims were primarily exploratory. We examined a series of variables linked in the literature with rapid cycling and other variables of interest, including demographic features, familiality, bipolar subtype, age at onset, hypersensitivity to antidepressant drug therapy, thyroid disease, and markers of clinical complexity, including psychosis, hospitalizations, suicide attempts, and comorbid psychiatric disorders. The aims of this study are thus not only to test factors previously associated with rapid cycling but also to determine whether the core phenomenon of rapid switching has significant clinical implications on its own.

METHODS

PARTICIPANTS

Background and detailed methods for the National Institute of Mental Health Bipolar Disorder Genetics Initiative are described elsewhere.[28] Minimal entry requirements for a family were a proband with bipolar I disorder and at least 1 other first-degree relative with bipolar I disorder or schizoaffective disorder, bipolar type. This study was approved by the institutional review boards of the 4 participating sites (Indiana University, The Johns Hopkins University, the National Institute of Mental Health, and Washington University). After giving written informed consent, all of the participants were administered the Diagnostic Interview for Genetic Studies version 2.0[30] by trained interviewers. Best-estimate diagnoses were made by 2 noninterviewing psychiatrists (J.R.D., E.G., D.F.M., J.I.N., T.R., and others) on the basis of the interview, available medical records, and family history data. For this study, we used the *Research Diagnostic Criteria for a Selected Group of Functional Disorders*[31] for major affective disorder diagnoses and *DSM-III-R* for other psychiatric disorders. During the diagnostic interview, individuals completing the section on mania were asked: "Have you ever switched back and forth quickly between feeling high to feeling normal or depressed?" Participants responding in the affirmative were then asked whether the switches had occurred every few hours, days, or weeks. These questions defined rapid switching for our analysis. Because inspection of the data revealed only trivial differences between individuals with switching over hours vs days vs weeks, we did not report on data broken down by switching frequency, except where noted.

ANALYSIS

Bipolar disorder was given as the best-estimate diagnosis in 718 interviewed individuals from 208 families. Of these 718 individuals, 115 did not supply sufficient information about rapid switching and so were excluded from the analysis, including 3 individuals who reported rapid switching but could not state the frequency of switching. Of the remaining 603 individuals, 76% had bipolar I disorder, 17% had bipolar II disorder with recurrent major depressions, and 7% had schizoaffective disorder, bipolar type (individuals with hypomanias plus a single episode of major depression were not included).

Evaluation of familial risk for rapid switching was conducted in 2 ways. We included data on the risk to relatives given a proband with rapid switching, that is, the conventional family study method, and also data on the existence for any given individual of a relative with rapid switching. The rationale for reporting and using in the regression analysis the latter, unconventional measure of familial risk was that inclusion in the regression analysis of familial risk based on proband status would require that we exclude probands from the analysis.

To assess the relative utility of rapid switching as a marker for clinical heterogeneity vs conventional rapid cycling, we reanalyzed selected variables in individuals who provided a response to the following Diagnostic Interview for Genetic Studies question: "Have you had at least four episodes of mood disorder within a one-year period?" Rapid cycling by strict *DSM-IV* criteria could not be determined because no information was obtained on duration of episodes or remissions between episodes; thus, when discussing our "rapid-cycling" data we use the term "rapid cycling/4 episodes." We included in this analysis the 583 of 603 individuals who provided this information.

Group differences in sex distribution, comorbid diagnosis, and other binary phenomena were calculated using odds ratios (ORs) with 95% confidence intervals (CIs). Statistical significance for group differences was defined as a 95% CI excluding 1. Continuous variables were tested using the *t* test. One variable,

Table 1. Demographic Comparison of 603 Family Members With Bipolar Disorder With and Without Rapid Switching

Characteristic	No Rapid Switching (n = 335)	Rapid Switching (n = 268)	OR (95% CI)	*t* Test	*df*	*P* Value
Relative with rapid switching, No. (%)	200 (60)	202 (75)	2.07 (1.45-2.94)	NA	NA	NA
Female sex, No. (%)	194 (58)	167 (62)	1.20 (0.87-1.67)	NA	NA	NA
Never worked/currently disabled, No. (%)	20 (6)	14 (5)	0.87 (0.43-1.75)	NA	NA	NA
Marital status, No. (%)*						
Married/widowed	171 (52)	118 (44)				
Separated/divorced	77 (23)	68 (26)	0.74 (0.53-1.02)†	NA	NA	NA
Never married	82 (25)	81 (30)				
Education level, No. (%)						
High school or less	112 (34)	117 (44)				
Some college or graduated	159 (47)	115 (43)	1.54 (1.11-2.15)‡	NA	NA	NA
Beyond college	64 (19)	36 (13)				
Age at interview, mean (SD), y	43.4 (15.0)	37.6 (11.9)	NA	5.21	601	<.001
Education, mean (SD), y	14.2 (3.05)	13.3 (2.98)	NA	3.84	601	<.001

Abbreviations: CI, confidence interval; NA, not applicable; OR, odds ratio.
*Information was not available for all 603 individuals.
†Married/widowed vs separated/divorced and never married combined.
‡High school or less vs some college or graduated and beyond college combined.

number of bipolar episodes, was evaluated using the Mann-Whitney test because data for number of episodes was an overall estimate of depressive, manic, and hypomanic episodes provided by the interviewees, and episodes too numerous to count were coded as "99" by interviewers because of data entry requirements. Thus, a valid mean number of episodes could not be calculated. Statistical significance for both analyses of continuous variables was defined as $P<.05$. Hypothesis testing of an association with rapid switching across relevant variables was performed using logistic regression analysis. Logistic regression analyses were performed with generalized estimating equations[32] to take into account potential correlations between data for multiple members of the same family. Odds ratios and *P* values are reported for these analyses, with statistical significance defined as $P<.05$ or a 95% CI excluding 1.

RESULTS

Nearly half (44%) of the 603 family members with bipolar disorder who provided any information about rapid switching reported that they had "switched back and forth quickly between feeling high to feeling normal or depressed" at some time in their illness. Two fifths of these rapid-switching individuals (40%) reported that switching occurred over the course of every few hours, another two fifths (41%) switched every few days, and the remainder switched over the course of weeks.

Relatives with and without rapid switching seemed similar on most demographic measures, including sex, occupational disability, and marital status (**Table 1**). Individuals with rapid switching were more likely to have a relative who reported rapid switching on interview than were individuals without rapid switching (75% vs 60%). However, risk of rapid switching in relatives of probands with rapid switching was only slightly higher than that in relatives without a rapid-switching proband, that is, 47% of those with vs 38% of those without a rapid-switching proband had rapid switching themselves (OR, 1.44; 95% CI, 0.97-2.13). Rapid-switching individuals were younger at the time of interview and had approximately 1 less year of education than those without rapid switching.

Rapid-switching individuals had significantly more episodes of mania, depression, and hypomania than did individuals without rapid switching (**Table 2**). Per year of bipolar illness, individuals with rapid switching had an (estimated) mean (SD) of 4.5 (5.7) episodes vs 2.4 (6.9) episodes per year for those without rapid switching ($t_{580}=3.99$; $P<.001$). There was significant overlap with rapid cycling/4 episodes: 76% of individuals with rapid switching had rapid cycling/4 episodes (the other 24% presumably having <4 full episodes in a year) vs 20% of those without rapid switching (who may have had ≥4 episodes with remissions or gradual transitions). Rapid-switching individuals had a significantly lower mean age at onset of bipolar disorder than individuals without rapid switching (17 vs 22 years) and accordingly a lower mean age at first treatment (21 vs 25 years). Individuals with rapid switching had been prescribed greater than 1.5 times as many different antidepressant agents and were twice as likely to indicate that they had experienced high moods and energy associated with the onset of antidepressant drug therapy as individuals without rapid switching. There seemed to be no systematic difference in the distribution of bipolar diagnostic subtypes across rapid-switching frequencies: approximately 1 in 6 individuals in either group had bipolar II disorder with recurrent major depression.

Rates of psychiatric comorbidity were 1.5 to 2 times higher in individuals with rapid switching across a variety of comorbid anxiety and substance abuse disorders, individually and collectively (**Table 3**). Eating disorders were more than twice as common in individuals with rapid switching as in those without. Hypothyroidism was somewhat, but not significantly, more common in individuals with rapid switching (15% vs 10%).

Individuals with rapid switching were more likely to have attempted suicide (42% vs 27%) and tended to have 1 more hospitalization than individuals who had bipolar disorder without rapid switching (**Table 4**). On

Table 2. Characteristics of Bipolar Disorder in 603 Individuals With and Without Rapid Switching

Characteristic	No Rapid Switching (n = 335)	Rapid Switching (n = 268)	OR (95% CI)	*t* Test	*df*	*P* Value
Bipolar disorder subdiagnosis, No. (%)						
Bipolar II with recurrent depression	62 (19)	43 (16)				
Bipolar I	255 (76)	201 (75)	0.84 (0.55-1.29)*	NA	NA	NA
Schizoaffective, bipolar type	18 (5)	24 (9)				
Rapid cycling†‡	65 (20)	197 (76)	12.92 (8.70-19.18)	NA	NA	NA
Psychosis with affective episode	133 (40)	122 (46)	1.27 (0.92-1.76)	NA	NA	NA
Antidepressant-associated high†	53 (19)	99 (41)	2.95 (1.99-4.38)	NA	NA	NA
Episodes of mania, hypomania, or depression, median (25th-75th quartile), No.†	9 (4-29)	47 (11-110.5)	NA	–9.29§	NA	<.001
Age at onset of bipolar disorder, mean (SD), y	22.43 (9.29)	17.02 (7.86)	NA	7.60	601	<.001
Age at first outpatient treatment, mean (SD), y†	25.26 (9.41)	21.39 (9.55)	NA	4.88	579	<.001
Antidepressants tried, mean (SD), No.	1.33 (1.72)	2.09 (2.51)	NA	–4.38	601	<.001

Abbreviations: CI, confidence interval; NA, not applicable; OR, odds ratio.
*Bipolar II vs bipolar I and schizoaffective, bipolar combined.
†Information was not available for all 603 individuals.
‡Broadly defined as 4 episodes per year, without regard to episode duration or intraepisode remission.
§*z* Statistic.

Table 3. Selected Comorbid Disorders With Bipolar Disorder in 603 Family Members With and Without Rapid Switching*

Disorder	No Rapid Switching (n = 335)	Rapid Switching (n = 268)	OR (95% CI)
Substance abuse or dependence			
Alcohol abuse or dependence	108 (32)	136 (51)	2.17 (1.55-3.02)
Cocaine/amphetamine abuse or dependence	30 (9)	45 (17)	2.05 (1.25-3.36)
Any drug abuse or dependence	74 (22)	91 (34)	1.81 (1.26-2.60)
Any substance abuse or dependence	133 (40)	158 (59)	2.18 (1.57-3.03)
Anxiety disorders			
Panic disorder	41 (12)	66 (25)	2.34 (1.53-3.60)
Social phobia, simple phobia, or agoraphobia	27 (8)	51 (19)	2.68 (1.63-4.41)
Obsessive-compulsive disorder	7 (2)	17 (6)	3.17 (1.30-7.77)
Any anxiety disorder	68 (20)	105 (39)	2.53 (1.76-3.63)
Eating disorder	13 (4)	28 (10)	2.89 (1.47-5.70)
Hypothyroid disorder	34 (10)	40 (15)	1.55 (0.95-2.53)

Abbreviations: CI, confidence interval; OR, odds ratio.
*Data are given as number (percentage) of individuals.

average, individuals with rapid switching had made greater than 1.5 suicide attempts each (including individuals who never attempted suicide) vs a rate of less than 0.6 in those without rapid switching.

Based on previous research into clinical and demographic factors associated with rapid switching and with patterns observed in our data, we constructed a logistic regression model incorporating sex, education level, genetic risk (ie, whether the individual had a relative with rapid switching), self-report of antidepressant-triggered manic symptoms, thyroid disease, and age at onset of bipolar disorder (earliest of age at first depression, mania, or hypomania). Of these variables, only sex and thyroid disease did not show a significant association with rapid switching (**Table 5**). Thus, early age at onset (the strongest association occurred in the youngest age group, with onset before 15 years), familial rapid switching, and antidepressant-triggered manic symptoms all were associated with rapid switching, taking into account each of the other variables and intrafamilial correlation.

We then performed logistic regression analyses to determine how rapid switching may be associated with other outcomes examined in the preliminary analysis, including anxiety and substance abuse or dependence comorbidity and having ever attempted suicide. For these analyses, we stratified individuals with rapid switching by the reported switch frequency (hours, days, or weeks). In the case of anxiety disorders, female sex was associated, and rapid switching over a frequency of hours (OR, 2.65; 95% CI, 1.65-4.3) or days (OR, 3.2; 95% CI, 2.0-5.1), but not weeks, was also associated with anxiety disorder comorbidity, taking into account sex. Substance abuse disorders were associated with male sex and with all frequencies of rapid switching.

To evaluate the potential effect of comorbidity and other variables associated with rapid switching on risk of suicide, we ran the analysis with an expanded model for suicide risk including substance abuse or dependence, anxiety disorder comorbidity, education, and age at onset variables as well as sex and cycle frequencies of hours or days. In this model, childhood-onset (<15 years) bipolar disorder was the strongest risk factor for suicide attempts (OR, 2.2; 95% CI, 1.3-3.7), and rapid switching over hours (OR, 1.8; 95% CI, 1.2-2.7), but not days

Table 4. Suicide Attempts and Psychiatric Hospitalizations in 603 Family Members With Bipolar Disorder With and Without Rapid Switching

Variable	No Rapid Switching (n = 335)	Rapid Switching (n = 268)	OR (95% CI)	*t* Test	*df*	*P* Value
Ever attempted suicide, No. (%)*	90 (27)	112 (42)	1.91 (1.36-2.70)	NA	NA	NA
Ever hospitalized, No. (%)*	247 (75)	193 (73)	0.92 (0.64-1.34)	NA	NA	NA
Suicide attempts, mean (SD), No.	0.58 (1.44)	1.52 (4.41)	NA	–3.67	601	<.001
Psychiatric hospitalizations, mean (SD), No.	3.29 (6.83)	4.27 (8.71)	NA	–1.54	601	≤.12

Abbreviations: CI, confidence interval; NA, not applicable; OR, odds ratio.
*Information was not available for all 603 individuals.

Table 5. Odds in 603 Family Members With Bipolar Disorder of Reporting Rapid Switching Given Selected Characteristics: Logistic Regression Analysis Using Generalized Estimated Equations

Characteristic	Odds Ratio (95% CI)	SE	*z* Statistic	*P* Value
Female sex	1.01 (0.69-1.49)	0.20	0.05	≤.96
Relative with rapid switching	2.94 (1.98-4.37)	0.59	5.34	≤.001
Antidepressant-associated high	2.49 (1.66-3.73)	0.51	4.40	≤.001
Thyroid disease	1.40 (0.85-2.30)	0.35	1.33	≤.18
Age at bipolar onset 15-24 y*	4.04 (2.46-6.64)	1.02	5.52	≤.001
Age at bipolar onset <15 y*	7.14 (4.04-12.62)	2.08	6.76	≤.001
Post–high school education	0.70 (0.48-1.00)	0.13	–1.95	≤.051

Abbreviation: CI, confidence interval.
*Compared with age at onset of greater than 25 years.

Table 6. Rapid Cycling* and Selected Characteristics Associated With the Phenomenon of Rapid Switching

Characteristic	No Rapid Cycling (n = 321)	Rapid Cycling (n = 262)	Unknown Rapid Cycling (n = 20)	Rapid Cycling vs No Rapid Cycling OR (95% CI)	*t* Test	*df*	*P* Value	Rapid-Switching Statistic†
Female sex, No. (%)	184 (57)	167 (64)	10 (50)	1.31 (0.94-1.83)	NA	NA	NA	1.20‡
Bipolar II diagnosis, No. (%)	52 (16)	49 (19)	4 (20)	1.19 (0.77-1.83)	NA	NA	NA	0.84‡
Rapid switching, No. (%)	61 (19)	197 (75)	10 (50)	12.92 (8.70-19.18)	NA	NA	NA	NA
Antidepressant-associated high, No. (%)	55 (17)	93 (35)	4 (20)	2.28 (1.54-3.38)	NA	NA	NA	2.95‡
Any substance abuse, No. (%)	136 (42)	143 (55)	12 (60)	1.63 (1.18-2.27)	NA	NA	NA	2.18‡
Any anxiety disorder, No. (%)	73 (23)	96 (37)	4 (20)	1.96 (1.37-2.82)	NA	NA	NA	2.53‡
Hypothyroid disorder, No. (%)	51 (16)	55 (21)	0	1.38 (0.85-2.25)	NA	NA	NA	1.55‡
Ever attempted suicide, No. (%)	89 (28)	108 (41)	5 (25)	1.81 (1.28-2.56)	NA	NA	NA	1.91‡
Education, mean (SD), y	14.2 (3.1)	13.3 (2.9)	14.9 (2.8)	NA	3.51	581	<.001	3.84§
Age at onset of bipolar disorder, mean (SD), y	22.2 (9.6)	17.3 (7.7)	19.7 (8.4)	NA	6.73	581	<.001	7.60§
Antidepressants tried, mean (SD), No.	1.2 (1.6)	2.1 (2.5)	2.5 (2.4)	NA	–5.14	581	<.001	–4.38§
Suicide attempts, mean (SD), No.	0.7 (2.6)	1.4 (3.8)	0.6 (1.1)	NA	–2.50	581	.01	–3.67§
Psychiatric hospitalizations, mean (SD), y	2.9 (3.9)	4.7 (10.8)	3.9 (3.7)	NA	–2.86	581	.004	–1.54§

Abbreviations: CI, confidence interval; NA, not applicable; OR, odds ratio.
*Broadly defined as 4 episodes per year, without regard to episode duration or intraepisode remission.
†Statistic of selected comparable results from Tables 1 through 4.
‡Odds ratio.
§*t* Test.

(*P*=.14), and female sex (*P*=.001) were also significantly associated with suicide attempts, taking into account other variables. Substance abuse or dependence (*P*=.09) and anxiety disorder comorbidity (*P*=.88) did not significantly affect suicide risk in this model.

As noted previously, the groups defined by rapid switching and by rapid cycling/4 episodes overlapped significantly but were not identical. In our reanalysis of the key findings associated with rapid switching, the associations with rapid cycling/4 episodes all trended the same as in rapid switching but were, in most cases, slightly less robust (**Table 6**).

The 115 individuals who did not provide information about rapid switching composed a heterogeneous group. Seventy-five of the individuals were not interviewed about rapid switching because their negative responses to screening questions prompted interviewers to omit detailed questions about mania. Of these, 50 ultimately were diagnosed as having bipolar II disorder and 25 were given a best-estimate diagnosis of bipolar I dis-

order or schizoaffective disorder, bipolar type, on the basis of family history and medical records. The remaining 40 individuals included 15 who were queried in detail about mania but provided little information and 25 who provided information about other manic symptoms but were unable to answer questions about rapid switching. In these 115 individuals, there was a slightly higher proportion of males (46%) and a similar education level but an older age at interview (48 vs 41 years) compared with individuals who provided information about rapid switching. The proportion of these individuals who had relatives with rapid switching was nearly the same as that in relatives with known rapid switching. The age at onset of bipolar disorder for individuals without information on rapid switching was slightly higher at 24.4 years, and the median number of lifetime bipolar disorder episodes (n=11) was consistent with the entire sample. Measures of clinical severity and outcome reflected a less severe course, with fewer of these individuals reporting a suicide attempt (19%) or hospitalization (58%) than individuals who provided information about rapid switching (see Tables 1, 2, and 4 for comparisons).

COMMENT

A large proportion of family members with bipolar disorder reported that they had "switched back and forth quickly between feeling high and feeling normal or depressed" at some time in the course of their illness. Our results support the hypothesis that individual responses to this item on the diagnostic interview denote a distinct course of illness, with significant variation in age at onset, suicide risk, and comorbid complications compared with the illness in individuals who did not experience rapid switching. First we will examine these associations in more detail, and then we will discuss the possible implications of these findings for research.

Our strongest finding was the association of childhood and early adult onset of bipolar disorder with rapid switching. These results indirectly support findings from studies[33-35] of the clinical presentation of bipolar disorder in children and adolescents, in whom complex and rapidly shifting affective states may be the modal pattern. As noted previously, very early onset of bipolar disorder produced the highest risk of rapid switching and of suicide attempts in this analysis. We did not have the data to determine whether rapid switching begins during adolescence in early-onset cases. Whether the vulnerability to rapid switching causes earlier emergence of mania and depression or whether early mania and depression leads to an unstable course of illness remains in question.

Suicide and rapid cycling or switching do not seem to have been linked in the literature previously.[36] Their association in our data suggests a similarity of extremely high-frequency switching to a bipolar mixed state, which can place patients at high risk for suicidal behavior.[37,38] It remains to be seen whether the mixture or alternation of agitation and despondency provokes suicidal behavior or whether suicidal behavior arises from the difficulty of managing these conditions therapeutically. The association of rapid switching with antidepressant drug use must be interpreted with similar caution because treatment-resistant patients tend to be prescribed a wider variety of antidepressants. In a similar vein, although antidepressant-associated manic symptoms occurred in more than 40% of individuals with rapid switching,[39] apparently supporting the role of antidepressant drug therapy as a trigger for rapid switching, the emergence of manic symptoms after initiation of antidepressant drug treatment might be coincidental if the mood is shifting rapidly on its own.

Our data on comorbidity with rapid switching are consistent with previous reports of high rates of substance abuse or dependence and anxiety disorder comorbidity with rapid switching in a treatment study population.[40] A large medical record review study[41] of bipolar patients found an association of substance abuse with frequent panic attacks and with daily and hourly cycling (but not *DSM-IV* rapid cycling). In the latter study, as in an earlier study,[42] substance abuse with bipolar disorder was also associated with a significantly younger age at onset of bipolar disorder. Echoes of these results in our own analyses suggest that an early-onset/rapid-switching form of bipolar disorder heightens the vulnerability to substance abuse and anxiety disorders, results from having comorbid disorders, or together compose a variant form of bipolar disorder.

We found mild evidence in the logistic regression analysis for the hypothesis that rapid switching denotes a familial variant of bipolar disorder, in contrast to several negative studies.[6,43,44] Our finding must be interpreted with caution because the analysis for familial risk using standard family study methods yielded an association without statistical significance. The association of rapid switching with panic disorder may imply a stronger genetic factor than we could detect. In this data set[29] and at least 1 other,[45] bipolar and panic disorder comorbidity aggregated in some families. Additional analysis of the present data set has shown increased risk for rapid switching in families with high rates of panic disorder.[46] Thus, panic and rapid switching may together define a familial bipolar subtype. A possible common genetic cause for panic and rapid switching might involve a protein that fails to modulate rapid affective changes, resulting in either polarity shifts or panic attacks. One potential candidate, again, is catecholamine-*O*-methyltransferase, which has been linked to panic disorder in 2 studies.[47,48]

Whereas some researchers[8,49] have found that rapid cycling is seen predominantly in patients with bipolar II disorder, we detected no elevated risk for rapid switching or rapid cycling/4 episodes associated with bipolar II disorder. Comparison of our sample with others is problematic, however, as we did not draw primarily from a clinical population, in which individuals with bipolar II disorder and rapid cycling might be overrepresented as a result of having greater clinical acuity than their counterparts without rapid cycling. Moreover, many interviewees with hypomania in our families were systematically excluded from answering questions about rapid switching or cycling by interview design. The lack of an association of rapid switching with female sex also may be a consequence of studying a nonclinical population. With respect to the weak association with hypothyroidism, we could not detect

subclinical thyroid abnormalities using our methods, so our negative finding is inconclusive.

A limitation of this study is the design, which was cross-sectional, retrospective, and not aimed to uncover detailed information about rapid switching. Thus, beyond demonstrating the potential for the simple phenomenon of rapid switching to predict differences in course and complications of bipolar disorder, we can say little else about the phenomenon of rapid switching in our study participants. Another limitation is that data were not gathered on rapid switching in many individuals with bipolar disorder. Although the large amount of missing data may raise questions about the stability of the results if we had collected the relevant information, there is no indication that these data, if available, would have skewed the results in a systematic way. Prospective and longitudinal studies of patients with childhood- and adolescent-onset bipolar disorder, with specific attention to rapid switching, are essential to validate and extend our results.

Beyond frequency of switching, there may be other salient aspects to rapid switching than were available in our data, including the age when rapid switching occurred, the duration of rapid switching, personality vulnerability and life events that triggered emotional lability, the direct link of a rapid-switching period to antidepressant drug treatment or substance abuse, and the relationship with episodes of illness. Rapid switching within an episode of mania might be considered a mixed state, whereas rapid switching between episodes of mania and depression might be considered cyclothymia. The Diagnostic Interview for Genetic Studies (version 2.0) lacks a section on cyclothymic disorder, which has been linked to the likelihood of switching from unipolar to bipolar disorder if not to rapid cycling itself.[50]

We contend that rapid switching of mood is the core phenomenon behind much of what has been variously termed *DSM-III-R* mixed mania, borderline emotional lability, truncated or complex or ultra-rapid cycling, and perhaps other such concepts in the literature. Participants in the present study seemed to be able to differentiate rapid switching from rapid cycling/4 episodes, as more than 100 of them answered these questions discordantly. As a practical matter, it is simpler to ask patients and research participants about the experience of rapid switching of mood states than to assess whether they have had 4 discrete episodes in a year. The results of this study suggest that it may be worthwhile to ask patients and bipolar disorder study participants about rapid switching because rapid switching (1) is at least as powerful as rapid cycling at marking a distinctive and more complicated course of bipolar illness, (2) defines a relatively unambiguous phenomenon, and (3) can be discovered using a simple question.

The main findings of this study are that rapid switching in familial bipolar disorder is common and is associated with early age at onset of bipolar disorder, greater substance abuse and anxiety comorbidity, and greater risk of suicidal behavior compared with bipolar disorder without rapid switching. Because these associations imply a more clinically complex course, we conclude that the phenomena of rapid polarity shifts and mood instability may be as important to study as *DSM-IV*–defined rapid cycling as we attempt to understand the fundamental pathologic processes behind specific symptoms and subtypes of bipolar disorder.

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Corresponding author and reprints: Dean F. MacKinnon, MD, Department of Psychiatry and Behavioral Sciences, The Johns Hopkins University School of Medicine, Meyer 3-181, 600 N Wolfe St, Baltimore, MD 21287 (e-mail: dmackin@jhmi.edu).

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