Clinical Expression of Bipolar Disorder Type I as a Function of Age and Polarity at Onset: Convergent Findings in Samples From France and the United States

Bruno Etain, MD, PhD; Mohamed Lajnef, MStat; Frank Bellivier, MD, PhD; Flavie Mathieu, PhD; Aurélie Raust, Psych; Barbara Cochet, Psych; Sébastien Gard, MD; Katia M'Bailara, PhD; Jean-Pierre Kahn, MD, PhD; Orly Elgrabli, Psych; Renaud Cohen, Psych; Stéphane Jamain, PhD; Eduard Vieta, MD, PhD; Marion Leboyer, MD, PhD; and Chantal Henry, MD, PhD

ABSTRACT

Background: The clinical presentation, course, and comorbidities of bipolar disorder type I are highly heterogeneous, and this variability remains poorly predictable. Certain onset characteristics (eg, age and polarity at onset) may delineate subgroups differing in clinical expression and outcome.

Method: We retrospectively investigated the association between both age and polarity at onset and the clinical characteristics of bipolar I disorder (*DSM-IV*) in 2 independent adult samples: 480 French patients assessed in 1992–2006 (patients had been recruited from 3 university-affiliated psychiatry departments) and 714 US patients assessed in 1991–2003 (data were extracted from the Bipolar Disorder Phenome Database).

Results: Polarity at onset correlated with subsequent predominance ($P < .001$). Most patients experienced a depressive onset (57.9% in France vs 71.0% in the United States; $P < .001$) associated with a higher density of depressive episodes, suicidal behavior, and alcohol misuse. A manic onset was associated with a higher density of manic episodes. Early onset was frequent in both countries (42% in France vs 68% in the United States; $P < .001$) and was associated with suicidal behavior and cannabis and cocaine/opiate misuse. Sensitivity for the prediction of clinical characteristics was 1%–35% for age at onset and 26%–47% for polarity at onset.

Conclusions: Onset characteristics are associated with subsequent predominant polarity, suicidal behavior, and substance misuse in bipolar I disorder. These findings may facilitate personalized treatment strategies based on type of onset and may also facilitate early focused strategies for preventing comorbidity. Given the relatively low sensitivity and specificity of these onset characteristics for predicting clinical variables, the relevance of age and polarity at onset as specifiers in nosographical classifications will require further studies. However, polarity at onset may be the more relevant specifier, with further investigation required for age at onset.

J Clin Psychiatry 2012;73(4):e561–e566

Submitted: *August 17, 2010; accepted October 31, 2011 (doi:10.4088/JCP.10m06504).*
Corresponding author: *Bruno Etain, MD, PhD, Pôle de Psychiatrie, Hôpital Albert Chenevier, 40, rue de Mesly, 94000 Créteil Cedex, France (bruno.etain@inserm.fr).*

Bipolar disorder type I is highly heterogeneous in terms of its clinical expression, course, comorbid psychiatric disorders, comorbid medical conditions, and treatment response.[1] The factors underlying this variability are poorly understood. Nevertheless, recent studies have suggested that some onset characteristics, such as age and polarity at the first mood episode, may be associated with different patterns of clinical expression, course, and comorbid conditions.[2–4] This observation may have major implications for the development of preventive strategies, clinical management, and drug prescription.

Age at onset (ie, age at the first major mood episode) is probably the associated factor most widely studied to date (for review, see Leboyer et al[2]). A threshold at about 21 years of age, defining an early-onset subgroup of the disorder, has consistently been identified in 7 independent bipolar I samples from Europe and the United States.[5–11] Early-onset bipolar I disorder has been associated with a particular pattern of clinical expression (psychotic features during episodes), a more severe course (rapid cycling), and a higher frequency of comorbid conditions (suicidal behavior, alcohol/substance misuse, and anxiety disorders) (for review, see Leboyer et al[2]).

The polarity of the first episode (ie, manic or depressive) may also be a relevant factor associated with the course of the disorder. It has been suggested that depressive onset is the most frequent[12–16] and is associated with suicide attempts,[12–17] a rapid-cycling course,[13,14] comorbid anxiety disorders,[15,18] and Axis II comorbid conditions.[12] A manic onset of the disease has been associated with lifetime psychotic symptoms,[12,13,16] comorbid alcohol misuse,[16] and substance misuse preceding onset.[12] Polarity at onset is also of particular importance because it has been shown to correlate with the predominant polarity of the disease.[12–16,18,19]

These results have led some authors to suggest that both polarity and age at onset should be added as specifiers in the future *DSM-5*, given their relevance to both the course and outcome of the disease.[3] Polarity and age at onset have essentially been studied independently, but depressive onset has been associated with an earlier age at onset.[14–16,20,21] Thus, to avoid a confounding bias due to these 2 factors being studied independently, we retrospectively investigated the relationship between both polarity and age at onset and the clinical, progressive, and comorbid expression of bipolar I disorder in 2 well-characterized independent samples of bipolar I patients from France and the United States.

© Copyright 2012 Physicians Postgraduate Press, Inc.

Clinical Points

- The initial presentation of bipolar disorder is mostly depressive and occurs early in adulthood.
- The initial polarity of bipolar disorder is associated with subsequent polarity.
- Both age and polarity at onset are associated with suicidal behavior and substance misuse.

METHOD

Patient Sample (France)

Adult patients meeting *DSM-IV*[22] criteria for bipolar I disorder were recruited from 3 university-affiliated psychiatry departments and interviewed by trained psychiatrists using the French version of the Diagnostic Interview for Genetic Studies (DIGS).[23,24] Patients were of French origin and were euthymic at inclusion (ie, having Mania Rating Scale[25] and Montgomery-Asberg Depression Rating Scale[26] scores of no more than 5). Written informed consent was obtained from participants. The local institutional review boards approved the 2 original studies.

Patient Sample (United States)

Clinical data were extracted from the Bipolar Disorder Phenome Database.[27] We selected only bipolar I patients on the basis of the best-estimate diagnosis reported in the database. The construction of the database, the review of interview items, the extraction from the original dataset, and the quality control of the database have been reported elsewhere.[27] Briefly, adult bipolar patients were ascertained for genetic linkage studies. Diagnosis (*DSM-IV*) was determined with either the Schedule for Affective Disorders and Schizophrenia-Lifetime Version (SADS)[28] or the DIGS.[23]

Definition of Age at Onset

In the French sample, age at onset was defined as the age at which the first mood episode occurred (depressive, manic, hypomanic, or mixed), according to *DSM-IV* criteria (determined by reviewing case notes and information from the DIGS).

In the US sample, age at onset was defined (using the DIGS or the SADS) as the age at which the first *DSM-IV*–criteria manic or depressive episode occurred, on the basis of the fields "age at first major depression" and "age at first mania," with the youngest age recorded taken as the age at onset. Hypomanic and mixed onsets were not taken into account because they were not recorded in the database.

Age at onset was classified into 2 groups: early age at onset (≤ 21 years) and later age at onset (> 21 years). This age threshold was selected on the basis of the replicated results of 7 independent admixture analyses in European and US bipolar I samples.[5–11]

Definition of Polarity at Onset

In the French sample, 2 types of onset polarity were defined: depressive onset (for which the first mood episode met *DSM-IV* criteria for a major depressive episode) and manic onset (for which the first mood episode met *DSM-IV* criteria for a manic, hypomanic, or mixed episode). In the US sample, polarity at onset was determined by comparing the reported age at the first major depressive episode and the age at the first manic episode (according to *DSM-IV* criteria). Subjects for whom the first major depressive episode and the first manic episode occurred at the same age were not included in the analysis. In the US sample, hypomanic and mixed onsets were not taken into account in the definition of polarity at onset because they were not recorded in the database.

Dependent Variables

Several clinical categorical and continuous variables were extracted from the 2 databases (France and United States). Categorical variables (suicidal behavior, mixed episodes, rapid cycling, psychotic symptoms, alcohol/drug misuse, and comorbid anxiety disorders) were categorized into lifetime presence versus absence. The term *misuse* defined the abuse of or dependence on substances. For continuous variables, a density measure was obtained by dividing the continuous variable (eg, number of events) by the duration of the disease (age at interview minus age at onset).

Statistical Analysis

We investigated the association of demographic and clinical characteristics with both age and polarity at onset. A logarithmic transformation of continuous variables (density of events per year of disease duration) was performed to achieve the normality assumed for parametric procedures. Generalized regression models adjusting for sex were then used to examine relationships between continuous variables and age and polarity at onset as independent variables. Associations between categorical dependent variables and independent variables (age and polarity at onset) were tested by logistic regression with adjustment for sex. As the analysis was exploratory, a P value of .05 or less was considered significant. For variables showing association in both samples, sensitivity and specificity were calculated (reported as the area under the curve [AUC] or as a percentage). Statistical analyses were performed with SAS software, version 9.1 (SAS Institute Inc, Cary, North Carolina).

RESULTS

Characteristics of the Samples

We studied 480 bipolar I patients from France and 714 bipolar I patients from the United States. The characteristics of the 2 samples differed significantly for numerous variables (Table 1); all differences remained significant when duration was used as a covariate (data not shown).

Table 1. Comparison of Demographic and Clinical Characteristics of the French and US Samples[a]

Characteristic	French Sample (N = 480)	US Sample (N = 714)	χ^2 or U Statistic	P Value[b]
Sex, female, n (%)	272 (56.7)	463 (64.8)	$\chi^2 = 8.11$	**.004**
Age at interview, mean (SD), y	41.9 (13.5)	41.1 (12.2)	$U = 0.98$	.33
Duration of illness, mean (SD), y	16.3 (11.7)	22.2 (12.12)	$U = -8.42$	**<.001**
No. of major episodes, mean (SD)	10.6 (24.4)	18.1 (20.6)	$U = -11.89$	**<.001**
No. of depressive episodes, mean (SD)	6.9 (17.4)	10.4 (13.5)	$U = -10.48$	**<.001**
No. of manic episodes, mean (SD)	4.3 (11.2)	8.1 (11.8)	$U = -9.73$	**<.001**
No. of hospitalizations, mean (SD)	4.7 (6.3)	4.1 (5.2)	$U = 3.56$	**<.001**
No. of suicide attempts, mean (SD)	2.4 (2.1)	2.9 (3.1)	$U = -2.01$	**.04**
Suicidal behavior, n (%)	203 (42.9)	282 (39.9)	$\chi^2 = 1.03$	.31
Rapid cycling, n (%)	53 (11.2)	277 (52.4)	$\chi^2 = 191.30$	**<.001**
Psychotic symptoms, n (%)	337 (70.8)	476 (68.4)	$\chi^2 = 0.77$	.38
Alcohol misuse, n (%)	101 (21.7)	283 (39.6)	$\chi^2 = 41.41$	**<.001**
Cannabis misuse, n (%)	66 (14.1)	135 (38.1)	$\chi^2 = 63.21$	**<.001**
Misuse of cocaine and opiates, n (%)	12 (2.5)	98 (13.7)	$\chi^2 = 43.21$	**<.001**
Panic disorder, n (%)	88 (19.0)	170 (23.8)	$\chi^2 = 3.83$	.06
Any anxiety disorder, n (%)	156 (39.8)	246 (37.6)	$\chi^2 = 0.49$	.48
Onset characteristics				
Depressive onset, n (%)	278 (57.9)	507 (71.0)	$\chi^2 = 21.82$	**<.001**
Age at onset, mean (SD), y	25.1 (10.1)	18.9 (8.7)	$U = 11.06$	**<.001**

[a]For each categorical variable, the percentage is expressed using the number of subjects for whom the information was available.
[b]Bolded P values indicate significance.

Table 2. Association Between Clinical Variables and Both Polarity and Age at Onset, Adjusted for Gender[a]

	French Sample (N = 480)				US Sample (N = 714)			
Clinical Variable	Manic Onset vs Depressive Onset, β (95% CI)[b]	P	Early Onset vs Late Onset, β (95% CI)[c]	P	Manic Onset vs Depressive Onset, β (95% CI)[b]	P	Early Onset vs Late Onset, β (95% CI)[c]	P
Quantitative variables[d]								
Major episodes[d]	−0.17 (−0.36 to 0.02)	.07	−0.16 (−0.35 to 0.02)	.08	0.05 (−0.14 to 0.23)	.62	0.35 (0.18 to 0.52)	<.001
Depressive episodes[d]	−0.25 (−0.46 to −0.03)	.02	−0.15 (−0.36 to 0.06)	.15	−0.35 (−0.55 to −0.15)	<.001	0.27 (0.08 to 0.45)	.004
Manic episodes[d]	0.36 (0.15 to 0.56)	<.001	−0.15 (−0.35 to 0.06)	.16	0.52 (0.33 to 0.71)	<.001	0.33 (0.18 to 0.55)	<.001
Hospitalizations[d]	0.14 (−0.04 to 0.33)	.12	−0.20 (−0.38 to −0.01)	.03	0.30 (0.08 to 0.52)	.007	−0.19 (−0.40 to 0.02)	.07
Suicide attempts[d]	0.26 (−0.02 to 0.55)	.07	−0.01 (−0.28 to 0.27)	.15	0.07 (−0.21 to 0.34)	.62	−0.11 (−0.39 to 0.17)	.45
Qualitative variables								
Suicidal behavior	−0.39 (−0.77 to −0.01)	.04	0.77 (0.39 to 1.15)	<.001	−0.42 (−0.78 to −0.06)	.02	0.72 (0.26 to 1.18)	<.001
Rapid cycling	−0.88 (−1.54 to −0.23)	.009	0.44 (−0.14 to 1.02)	.13	−0.35 (−0.74 to 0.03)	.07	0.83 (0.44 to 1.22)	<.001
Psychotic symptoms	0.38 (−0.03 to 0.79)	.07	0.31 (−0.10 to 0.72)	.13	0.44 (0.06 to 0.82)	.02	0.30 (−0.05 to 0.65)	.09
Alcohol misuse	−0.73 (−1.21 to −0.25)	.003	0.15 (−0.30 to 0.61)	.52	−0.38 (−0.73 to −0.02)	.04	0.56 (0.21 to 0.90)	.002
Cannabis misuse	−0.47 (−1.03 to −0.10)	.10	0.96 (0.41 to 1.50)	<.001	0.46 (−0.02 to 0.94)	.06	0.56 (0.02 to 1.10)	.04
Misuse of cocaine/opiates	−0.77 (−2.09 to −0.56)	.26	1.44 (0.12 to 2.76)	.03	0.33 (−0.14 to 0.80)	.17	1.00 (0.44 to 1.55)	<.001
Panic disorder	0.05 (−0.42 to −0.52)	.85	0.04 (−0.43 to 0.51)	.86	−0.46 (−0.89 to −0.03)	.03	0.62 (0.20 to 1.04)	.004
Any anxiety disorder	0.13 (−0.28 to 0.54)	.54	0.28 (−0.24 to 0.60)	.31	−0.59 (−0.97 to −0.21)	.003	0.66 (0.28 to 1.04)	.0007

[a]Gray cells indicate significant associations that were observed in both samples.
[b]A negative value for β indicates an association with depressive onset.
[c]A positive value for β indicates an association with early onset.
[d]All dependent variables were defined as the Log (density of events), the density of events being the number of events per year of disease.

Depressive onset was associated with an earlier age at onset in the US sample ($\chi^2 = 20.97$, $P < .001$), whereas no such association was observed in the French sample ($\chi^2 = 0.56$, $P = .45$).

Polarity at Onset

Most bipolar I patients experienced a depressive onset, and a depressive onset was much more frequent among US patients than among French patients (71.0% versus 57.9%, respectively; $\chi^2 = 21.82$, $P < .001$).

Several associations were observed in both samples (Table 2). A depressive onset was associated with a higher density of depressive episodes (France: $P = .02$, AUC = 0.68; United States: $P < .001$, AUC = 0.61), a lifetime presence of suicidal behavior (France: OR = 1.48; 95% CI, 1.01–2.16; sensitivity = 47%; specificity = 63%) (United States: OR = 1.52; 95% CI, 1.06–2.17; sensitivity = 44%; specificity = 70%), and lifetime alcohol misuse (France: OR = 2.08; 95% CI, 1.28–3.36; sensitivity = 26%; specificity = 85%) (United States: OR = 1.46; 95% CI, 1.032.08; sensitivity = 42%; specificity = 66%). A manic onset was associated with a higher density of manic episodes ($P < .001$ in both samples; $AUC_{France} = 0.59$; $AUC_{US} = 0.63$).

In the French sample, 61.3% of the mood episodes of bipolar patients who had experienced a depressive onset were major depressive episodes, whereas 60.1% of mood

© Copyright 2012 Physicians Postgraduate Press, Inc.

episodes in bipolar patients who had experienced a manic or hypomanic onset were manic or hypomanic. Similar percentages were observed for the US sample (61.3% and 57.8%, respectively). Thus, in both samples, polarity at onset (but not age at onset) was associated with the subsequent predominant polarity of the disease. Indeed, polarity at onset was the only variable found to be associated with this percentage (France: $\beta = -0.21$; 95% CI, −0.26 to −0.16; $P < .001$) (United States: $\beta = -0.19$; 95% CI, −0.23 to −0.15; $P < .001$).

Some associations were observed in only 1 sample. A depressive onset was associated with rapid cycling in the French sample only, and with panic disorder and anxiety disorders in the US sample only. A manic onset was associated with a higher density of hospitalizations in the US sample only.

Age at Onset

A large proportion of patients belonged to the early-onset subgroup in both the French and US samples (42% in the French sample versus 68% in the US sample; $P < .001$).

Several associations were observed in both samples (see Table 2). An early age at onset was associated with suicidal behavior (France: OR = 2.16; 95% CI, 1.48–3.15; sensitivity = 35%; specificity = 46%) (United States: OR = 2.05; 95% CI, 1.44–2.92; sensitivity = 27%; specificity = 54%), lifetime cannabis misuse (France: OR = 2.60; 95% CI, 1.51–4.48; sensitivity = 9%; specificity = 79%) (United States: OR = 1.75; 95% CI, 1.02–3.01; sensitivity = 30%; specificity = 59%), and lifetime cocaine/opiate misuse (France: OR = 4.21; 95% CI, 1.12–15.80; sensitivity = 1%; specificity = 95%) (United States: OR = 2.71; 95% CI, 1.55–4.73; sensitivity = 7%; specificity = 83%).

Some associations were observed in only 1 sample. An earlier onset was associated with a lower density of hospitalizations in the French sample only. An earlier onset was associated with a higher density of major episode (both depressive and manic), rapid cycling, alcohol misuse, panic disorder, and anxiety disorders in the US sample only.

DISCUSSION

In 2 large independent samples of bipolar I patients, we found that a depressive onset was the most frequent initial presentation of the disease and that polarity at onset was strongly correlated with the predominant polarity. We suggest that age and polarity at onset are associated with particular patterns of clinical expression, disease course, and comorbid conditions. Indeed, a depressive onset was associated with suicidal behavior and alcohol misuse, and earlier onset was associated with suicidal behavior and cannabis and cocaine/opiate misuse. These findings were obtained in 2 independent samples with different clinical presentations, recruitment procedures, geographic origins, levels of familial/genetic loading, ages at onset, and durations of illness. Furthermore, slightly different criteria were used to define age at onset and polarity at onset in the 2 samples. Nevertheless, despite these major differences, we found consistent associations in the 2 samples. These findings suggest that both age and polarity at onset should be systematically investigated in bipolar I patients and could be considered specifiers of the course of the disease, as previously proposed.[3]

In both samples, a major depressive episode was the most frequent mode of onset of bipolar I disorder, as previously suggested.[12–14] Therefore, most bipolar I patients will initially be thought to be suffering from a major depressive episode (single or recurrent) before the occurrence of the first manic, hypomanic, or mixed episode. This initial depressive presentation may account for the high estimated rate of misdiagnosis (about 70%)[29–32] and the long delay to treatment in many patients.[33] The awareness of psychiatrists and general practitioners should be increased, and they should be encouraged to explore in detail all possible indicators of a progression toward bipolar disorders when treating a patient suffering from a major depressive episode (particularly when recurrent). Careful screening for certain characteristics of major depressive episodes that have been identified as potential indicators of bipolar disease and for undiagnosed hypomanic episodes and family history of bipolar disorder should immediately trigger suspicion of possible progression toward bipolar disorders.[34]

Our second major finding for these 2 independent samples was the strong correlation between the polarity at onset of the disorder and subsequent predominant polarity, consistent with previous reports.[12–15,18,35] Polarity at onset is thought to be familial[21] and to be underpinned by genetic and/or shared environmental factors, accounting for the notion that polarity at onset reflects a more stable trait (ie, predominant polarity). This line of thought may have many implications for treatment. Indeed, the drug treatment strategy to be used could be anticipated early in the course of the disorder on the basis of polarity at onset. Some drugs may be significantly more effective at preventing manic relapses, whereas others may be better at preventing depressive symptoms.[36] Some adjustment of the serum concentrations of mood regulators may also be required as a function of polarity patterns. Lithium concentrations in the lower part of the therapeutic range may be sufficient for the optimal prevention of depressive episodes, whereas higher lithium concentrations, within the therapeutic range, may be required for optimal protection against manic/mixed episodes.[37–39]

In both samples, depressive onset was associated with suicidal behavior and alcohol misuse, as reported in previous studies.[12–17] An early onset was associated with suicidal behavior and misuse of cannabis or cocaine/opiates, as previously reported.[2,7,8] These findings suggest that careful and precise screening for substance use disorders and risks, as well as closer clinical monitoring, could help to prevent poor outcome (due to alcohol misuse and suicide attempts, in particular) in early-onset mood disorders.

This study was subject to several limitations. First, the determination of onset characteristics was based on retrospective assessment and may therefore be subject to recall bias. Second, the definition of polarity and age at onset differed slightly between samples, particularly in terms of the

© Copyright 2012 Physicians Postgraduate Press, Inc.

frequency of depressive polarity and early onset. Misclassifications may have occurred for some patients in the US sample, for which hypomanic and mixed-onset episodes were not recorded because they may be difficult to identify retrospectively.[13,15] Third, some associations were observed only in the US sample, and this lack of replication might be due to insufficient power because of the smaller size of the French sample. Finally, the samples differed in terms of clinical presentation. This difference may be due to the differences in recruitment procedures, geographic origins, level of genetic loading, age at onset, and duration of illness. As previously reported,[40,41] bipolar I patients from the United States have an earlier onset than patients from France. Indeed, the French sample was a mixture of sporadic cases (60%) and familial cases (40%), whereas all the US patients had at least 1 affected sibling; the US sample may therefore have been enriched in early-onset cases.[2] This difference may appear to be a limitation of the study. However, despite differences between the samples in the frequencies of depressive and/or earlier onset, several results were consistent between samples. This finding suggests that the principal associations observed between onset characteristics and subsequent course were robust.

The aim of this study was to determine whether onset characteristics were associated with the subsequent clinical expression of the disorder. The sensitivity and specificity of onset characteristics for predicting clinical variables appeared to be low. Indeed, the sensitivity of age at onset for predicting clinical characteristics ranged from 1% to 35% in the French sample and from 7% to 30% in the US sample. For polarity at onset, sensitivity was higher (26%–47%), with an AUC between 0.59 and 0.68, and specificity was acceptable (63%–85%). Given the sensitivity and specificity of each parameter, we can argue that many other factors may affect outcome, including duration of untreated illness, the appropriateness of treatment, and compliance with treatment. This issue could be addressed, at least in part, by making use of information about current psychotropic treatments and previous treatment sequences, but this information was not available in this study. Moreover, given the differences in sensitivity between the 2 factors considered, polarity at onset seems to have the better potential as a specifier, with further investigation required for age at onset.

CONCLUSION

Polarity at onset is associated with subsequent predominant polarity during the course of bipolar I disorder. Suicidal behavior and substance misuse are associated with both onset characteristics (ie, a depressive onset and an earlier age at onset). These findings are of particular interest for the identification of more homogeneous subgroups of patients for clinical and research studies, the definition of focused prevention strategies for comorbid conditions, and selection of the optimal and best targeted drugs for treatment. Our findings and those of previous studies provide evidence that onset polarity should be considered as a relevant specifier in future bipolar I classifications, as proposed for the *DSM-5*.[3] Age at onset, given its relatively low sensitivity for predicting clinical variables, requires further investigation to determine its potential relevance as a specifier.

Drug names: lithium (Lithobid and others).

Author affiliations: Institut national de la santé et de la recherche médicale (INSERM), Créteil, France (Drs Etain, Bellivier, Mathieu, Jamain, Leboyer, and Henry and Mr Lajnef); Pôle de Psychiatrie, APHP, Hôpital H. Mondor–A. Chenevier, Créteil, France (Drs Etain, Bellivier, Leboyer, and Henry and Mss Raust and Cochet); European Network of Bipolar Research Expert Centres (ENBREC), Paris, France (Drs Etain, Bellivier, Jamain, Vieta, Leboyer, and Henry); Université Paris Est, Faculté de médecine, Créteil, France (Drs Bellivier, Leboyer, and Henry); Service de psychiatrie adulte, Hôpital Charles Perrens, Bordeaux, France (Drs Gard and M'Bailara); Laboratoire de psychologie, Université Victor Segalen, Bordeaux, France (Dr M'Bailara); Service de Psychiatrie et Psychologie Clinique, Centre Hospitalier Universitaire de Nancy, Hôpital Jeanne-d'Arc, Toul, France (Dr Kahn, Ms Elgrabli, and Mr Cohen); and Bipolar Disorders Program, University of Barcelona, Hospital Clinic, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Barcelona, Spain (Dr Vieta).

Potential conflicts of interest: None reported.

Funding/support: This work was supported by INSERM, Paris, France; Assistance Publique-Hôpitaux de Paris, Paris, France; RTRS Santé Mentale (Fondation FondaMental), Créteil, France; Agence Nationale pour la Recherche (ANR), Paris, France; Fondation pour la Recherche sur le Cerveau (FRC), Paris, France; and National Alliance for Research on Schizophrenia and Depression (NARSAD), Great Neck, New York.

Acknowledgments: We thank Emmanuelle Abadie, research nurse, who helped monitor the data, and Marie-José Pereira, secretary, who helped draft the manuscript (both affiliated with Pôle de Psychiatrie, APHP, Hôpital H. Mondor–A. Chenevier, Créteil, France); Claudette Bulach, PharmD (RTRS Santé Mentale [Fondation FondaMental], Créteil, France), project manager in charge of ethical procedures; and Jean-Romain Richard, MSc (INSERM, Créteil, France), also in charge of ethical procedures. These acknowledged individuals have no conflicts of interest to declare. We are grateful to the bipolar patients and families who participated in and contributed to these studies. We thank the National Institute of Mental Health (NIMH) and James B. Potash, MD, MPH, for providing access to the Bipolar Disorder Phenome Database (http://bioinformoodics.jhmi.edu/gm/phenome/). Acknowledgments for collected data and biomaterials are as follows: Data and biomaterials were collected in 4 projects that participated in the NIMH Bipolar Disorder Genetics Initiative. From 1991–1998, the Principal Investigators and Co-Investigators were as follows: Indiana University, Indianapolis (U01 MH46282) (John Nurnberger, MD, PhD; Marvin Miller, MD; and Elizabeth Bowman, MD); Washington University, St. Louis, Missouri (U01 MH46280) (Theodore Reich, MD; Allison Goate, PhD; and John Rice, PhD); Johns Hopkins University, Baltimore, Maryland (U01 MH46274) (J. Raymond DePaulo, Jr, MD; Sylvia Simpson, MD, MPH; and Colin Stine, PhD); and NIMH Intramural Research Program, Clinical Neurogenetics Branch, Bethesda, Maryland (Elliot Gershon, MD; Diane Kazuba, BA; and Elizabeth Maxwell, MSW). Data and biomaterials were collected as part of 10 projects that participated in the NIMH Bipolar Disorder Genetics Initiative. From 1999–2003, the Principal Investigators and Co-Investigators were as follows: Indiana University, Indianapolis (R01 MH59545) (John Nurnberger, MD, PhD; Marvin J. Miller, MD; Elizabeth S. Bowman, MD; N. Leela Rau, MD; P. Ryan Moe, MD; Nalini Samavedy, MD; Rif El-Mallakh, MD, at University of Louisville; Husseini Manji, MD, at Wayne State University; Debra A. Glitz, MD, at Wayne State University; Eric T. Meyer, MS; Carrie Smiley, RN; Tatiana Foroud, PhD; Leah Flury, MS; Danielle M. Dick, PhD; Howard Edenberg, PhD); Washington University, St. Louis, Missouri (R01 MH059534) (John Rice, PhD; Theodore Reich, MD; Allison Goate, PhD; and Laura Bierut, MD); Johns Hopkins University, Baltimore, Maryland (R01 MH59533) (Melvin McInnis, MD; J. Raymond DePaulo, Jr, MD; Dean F. MacKinnon, MD; Francis M. Mondimore, MD; James B. Potash, MD; Peter P. Zandi, PhD; Dimitrios Avramopoulos; and Jennifer Payne); University of Pennsylvania, Philadelphia (R01 MH59553) (Wade Berrettini, MD, PhD); University of California at Irvine (R01 MH60068) (William Byerley, MD, and Mark Vawter, MD); University of Iowa, Iowa City (R01 MH059548) (William Coryell, MD, and Raymond Crowe, MD); University of Chicago, Illinois (R01 MH59535) (Elliot Gershon, MD; Judith Badner, PhD; Francis McMahon, MD; Chunyu Liu, PhD; Alan Sanders, MD; Maria Caserta;

Steven Dinwiddie, MD; Tu Nguyen; Donna Harakal); University of California at San Diego (R01 MH59567) (John Kelsoe, MD, and Rebecca McKinney, BA); Rush University, Chicago, Illinois (R01 MH059556) (William Scheftner, MD; Howard M. Kravitz, DO, MPH; Diana Marta, BS; Annette Vaughn-Brown, MSN, RN; and Laurie Bederow, MA); and NIMH Intramural Research Program, Bethesda, Maryland (1Z01MH002810-01) (Francis J. McMahon, MD; Layla Kassem, PsyD; Sevilla Detera-Wadleigh, PhD; Lisa Austin, PhD; and Dennis L. Murphy, MD). In addition, families were contributed by Dr. Carlos Pato at the University of Southern California and his staff. This work was sponsored by NIMH grants MH52618 and MH058693. Genotyping services were provided by the Center for Inherited Disease Research (CIDR). CIDR is fully funded through a federal contract from the National Institutes of Health to The Johns Hopkins University, Contract Number N01-HG-65403. Data and biomaterials were collected and supported by NIMH grant R01 MH59602 (to Miron Baron, MD) and by funds from the Columbia Genome Center, New York, New York, and the New York State Office of Mental Health. The main contributors to this work were Miron Baron, MD (Principal Investigator); Jean Endicott, PhD (Co–Principal Investigator); Jo Ellen Loth, MSW; John Nee, PhD; Richard Blumenthal, PhD; Lawrence Sharpe, MD; Barbara Lilliston, MSW; Melissa Smith, MA; and Kristine Trautman, MSW, all from the Department of Psychiatry, Columbia University, New York, New York. A small subset of the sample was collected in Israel in collaboration with Bernard Lerer, MD, and Kyra Kanyas, MS, from the Hadassah–Hebrew University Medical Center, Jerusalem, Israel. We are grateful to the patients and their family members for their cooperation and support, and to the treatment facilities and other organizations that collaborated with us in identifying families.

REFERENCES

1. Goodwin FK, Jamison KR. *Manic-Depressive Illness: Bipolar Disorders and Recurrent Depression*. 2nd ed. New York, NY: Oxford University Press Inc; 2007.
2. Leboyer M, Henry C, Paillere-Martinot ML, et al. Age at onset in bipolar affective disorders: a review. *Bipolar Disord*. 2005;7(2):111–118.
3. Colom F, Vieta E. The road to *DSM-V*: bipolar disorder episode and course specifiers. *Psychopathology*. 2009;42(4):209–218.
4. Tohen M, Frank E, Bowden CL, et al. The International Society for Bipolar Disorders (ISBD) Task Force report on the nomenclature of course and outcome in bipolar disorders. *Bipolar Disord*. 2009;11(5):453–473.
5. Bellivier F, Golmard JL, Henry C, et al. Admixture analysis of age at onset in bipolar I affective disorder. *Arch Gen Psychiatry*. 2001;58(5):510–512.
6. Bellivier F, Golmard JL, Rietschel M, et al. Age at onset in bipolar I affective disorder: further evidence for three subgroups. *Am J Psychiatry*. 2003;160(5):999–1001.
7. Hamshere ML, Gordon-Smith K, Forty L, et al. Age-at-onset in bipolar-I disorder: mixture analysis of 1369 cases identifies three distinct clinical sub-groups. *J Affect Disord*. 2009;116(1–2)23–29.
8. Lin PI, McInnis MG, Potash JB, et al. Clinical correlates and familial aggregation of age at onset in bipolar disorder. *Am J Psychiatry*. 2006; 163(2):240–246.
9. Manchia M, Lampus S, Chillotti C, et al. Age at onset in Sardinian bipolar I patients: evidence for three subgroups. *Bipolar Disord*. 2008;10(3): 443–446.
10. Severino G, Manchia M, Contu P, et al. Association study in a Sardinian sample between bipolar disorder and the nuclear receptor *REV-ERBα* gene, a critical component of the circadian clock system. *Bipolar Disord*. 2009; 11(2):215–220.
11. Tozzi F, Manchia M, Galwey NW, et al. Admixture analysis of age at onset in bipolar disorder. *Psychiatry Res*. 2011;185(1–2):27–32.
12. Daban C, Colom F, Sanchez-Moreno J, et al. Clinical correlates of first-episode polarity in bipolar disorder. *Compr Psychiatry*. 2006; 47(6):433–437.
13. Perugi G, Micheli C, Akiskal HS, et al. Polarity of the first episode, clinical characteristics, and course of manic depressive illness: a systematic retrospective investigation of 320 bipolar I patients. *Compr Psychiatry*. 2000;41(1):13–18.
14. Forty L, Jones L, Jones I, et al. Polarity at illness onset in bipolar I disorder and clinical course of illness. *Bipolar Disord*. 2009;11(1):82–88.
15. Perlis RH, Delbello MP, Miyahara S, et al; STEP-BD investigators. Revisiting depressive-prone bipolar disorder: polarity of initial mood episode and disease course among bipolar I Systematic Treatment Enhancement Program for Bipolar Disorder participants. *Biol Psychiatry*. 2005;58(7):549–553.
16. Chaudhury SR, Grunebaum MF, Galfalvy HC, et al. Does first episode polarity predict risk for suicide attempt in bipolar disorder? *J Affect Disord*. 2007;104(1–3):245–250.
17. Azorin JM, Kaladjian A, Adida M, et al. Risk factors associated with lifetime suicide attempts in bipolar I patients: findings from a French national cohort. *Compr Psychiatry*. 2009;50(2):115–120.
18. Colom F, Vieta E, Daban C, et al. Clinical and therapeutic implications of predominant polarity in bipolar disorder. *J Affect Disord*. 2006;93(1–3): 13–17.
19. Birmaher B, Axelson D, Goldstein B, et al. Four-year longitudinal course of children and adolescents with bipolar spectrum disorders: the Course and Outcome of Bipolar Youth (COBY) study. *Am J Psychiatry*. 2009; 166(7):795–804.
20. Edmonds LK, Mosley BJ, Admiraal AJ, et al. Familial bipolar disorder: preliminary results from the Otago Familial Bipolar Genetic Study. *Aust N Z J Psychiatry*. 1998;32(6):823–829.
21. Kassem L, Lopez V, Hedeker D, et al; Bipolar Disorder Consortium NIMH Genetics Initiative. Familiality of polarity at illness onset in bipolar affective disorder. *Am J Psychiatry*. 2006;163(10):1754–1759.
22. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition. Washington, DC: American Psychiatric Association; 1994.
23. Nurnberger JI Jr, Blehar MC, Kaufmann CA, et al. Diagnostic Interview for Genetic Studies: rationale, unique features, and training: NIMH Genetics Initiative. *Arch Gen Psychiatry*. 1994;51(11):849–859; discussion 863–844.
24. Preisig M, Fenton BT, Matthey ML, et al. Diagnostic Interview for Genetic Studies (DIGS): inter-rater and test-retest reliability of the French version. *Eur Arch Psychiatry Clin Neurosci*. 1999;249(4):174–179.
25. Bech P, Rafaelsen OJ, Kramp P, et al. The Mania Rating Scale: scale construction and inter-observer agreement. *Neuropharmacology*. 1978; 17(6):430–431.
26. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry*. 1979;134(4):382–389.
27. Potash JB, Toolan J, Steele J, et al; NIMH Genetics Initiative Bipolar Disorder Consortium. The Bipolar Disorder Phenome Database: a resource for genetic studies. *Am J Psychiatry*. 2007;164(8):1229–1237.
28. Endicott J, Spitzer RL. A diagnostic interview: the Schedule for Affective Disorders and Schizophrenia. *Arch Gen Psychiatry*. 1978;35(7):837–844.
29. Bowden CL. Strategies to reduce misdiagnosis of bipolar depression. *Psychiatr Serv*. 2001;52(1):51–55.
30. Perlis RH. Misdiagnosis of bipolar disorder. *Am J Manag Care*. 2005; 11(suppl):S271–S274.
31. Keck PE Jr, Kessler RC, Ross R. Clinical and economic effects of unrecognized or inadequately treated bipolar disorder. *J Psychiatr Pract*. 2008;14(suppl 2):31–38.
32. Fajutrao L, Locklear J, Priaulx J, et al. A systematic review of the evidence of the burden of bipolar disorder in Europe. *Clin Pract Epidemol Ment Health*. 2009;5(1):3.
33. Hirschfeld RM, Vornik LA. Recognition and diagnosis of bipolar disorder. *J Clin Psychiatry*. 2004;65(suppl 15):5–9.
34. Ghaemi SN, Ko JY, Goodwin FK. "Cade's disease" and beyond: misdiagnosis, antidepressant use, and a proposed definition for bipolar spectrum disorder. *Can J Psychiatry*. 2002;47(2):125–134.
35. Turvey CL, Coryell WH, Arndt S, et al. Polarity sequence, depression, and chronicity in bipolar I disorder. *J Nerv Ment Dis*. 1999;187(3):181–187.
36. Beynon S, Soares-Weiser K, Woolacott N, et al. Pharmacological interventions for the prevention of relapse in bipolar disorder: a systematic review of controlled trials. *J Psychopharmacol*. 2009;23(5):574–591.
37. Severus WE, Kleindienst N, Evoniuk G, et al. Is the polarity of relapse/ recurrence in bipolar-I disorder patients related to serum lithium levels? results from an empirical study. *J Affect Disord*. 2009;115(3):466–470.
38. Kleindienst N, Severus WE, Greil W. Are serum lithium levels related to the polarity of recurrence in bipolar disorders? evidence from a multicenter trial. *Int Clin Psychopharmacol*. 2007;22(3):125–131.
39. Kleindienst N, Severus WE, Möller HJ, et al. Is polarity of recurrence related to serum lithium level in patients with bipolar disorder? *Eur Arch Psychiatry Clin Neurosci*. 2005;255(1):72–74.
40. Post RM, Luckenbaugh DA, Leverich GS, et al. Incidence of childhood-onset bipolar illness in the USA and Europe. *Br J Psychiatry*. 2008;192(2): 150–151.
41. Baldessarini RJ, Bolzani L, Cruz N, et al. Onset-age of bipolar disorders at six international sites. *J Affect Disord*. 2010;121(1–2):143–146.