Eur Arch Psychiatry Clin Neurosci (2008) 258:497–504 DOI 10.1007/s00406-008-0823-x

ORIGINAL PAPER

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Toward the delineation of mania subtypes in the French National EPIMAN-II Mille Cohort

Comparisons with prior cluster analytic investigations

Received: 14 February 2008 / Accepted: 15 April 2008 / Published online: 20 June 2008

Abstract *Background* Knowledge about psychopathologic presentations of mania in current clinical practice has to be refined in order to improve diagnosis and treatment. *Methods* One thousand ninety manic patients included in the French National Study EPIMAN-II Mille were submitted to a cluster analysis on the basis of multiple variables related to the history of bipolar illness and symptoms of the current episode. *Results* Four clusters were identified: "classic mania" (29.3% of patients) with less severe mania; "psychotic mania" (22.7%) with psychotic symptoms, more severe mania, younger age and social impairment; "depressive mania" (30.4%) characterized by female gender, suicide attempts, high number of previous episodes and residual symptoms; and "dual mania" (17.6%) characterized by male gender, substance use, earlier onset and poor compliance. Patients groups also differed in manic symptoms, marital status, stressors preceding illness onset, prior diagnoses, first episode polarity and temperamental characteristics. *Limitations* Cross-sectional assessment of patients. *Conclusions* In comparing our findings with those of four prior cluster analytic studies, we integrate clinical characteristics of mania subtypes found in this very large representative French sample in contemporary practice, we suggest how such convergence of data may help improve earlier recognition, differential response to different treatments, and prevention of these subtypes. We finally suggest that such subtyping might provide clues to phenotype delineation suitable for pharmacogenetic investigations.

Key words cluster analysis · mania subtype · manic cluster

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Introduction

Despite noteworthy progress during the two last decades, accurate diagnosis and treatment of bipolar disorder is still an unmet need, as evidenced by the length of delay from symptom onset to recognition and use of mood stabilizers [26]. Many explanations have been put forward [28]. However, it could also be that aspects of bipolar illness itself are evolving due to changes in environment, culture, healthcare systems and treatment. It is therefore important to investigate the psychopathologic characteristics of mania in contemporary practice.

Most of our knowledge about the disorder is based on classic descriptions from previous centuries [14, 22, 33], which do not necessarily reflect present-day clinical practice. Large clinical–epidemiological stud-

ies, on the other hand, offer an opportunity to examine evolving presentations of bipolar disorder. These studies, which usually include a great number of patients and measures, are suitable to using multivariate statistics in order to address the question of heterogeneity of the disease. This approach, using a variety of analytic techniques, was successfully used with manic patients, yielding some evidence for new phenotypes which seem to fit current practice well [2, 19, 21, 27, 39, 42, 45].

The aim of the present study was to use the large databases of the EPIMAN-II-Mille French national cohort [11–13, 26] to explore further details of current mania subtypes using a cluster analytic approach, and then compare it with previous studies that have used this analytic strategy.

Methods

Study design

EPIMAN-II Mille, implemented in France, is a multisite naturalistic study of a systematic clinical assessment of hospitalized patients with acute manic episodes in the setting of "primary" bipolar disorder. The main objective of this study was to estimate the rates and test the validity of the different mania subtypes in a large sample of hospitalized patients. Our aim was to enrol 1,000 patients. To reach this goal, 317 psychiatrists each had to recruit at least two consecutive patients (with a maximum of six). All psychiatrists—working in public, university or private hospitals—were senior clinicians who had been specially trained to recognize mania according to the DSM-IV schema. The study was conducted between December 2000 and April 2002. At entry, screening of mania was made through the French version of the Structured Clinical Interview for DSM–IV (SCID) [16, 23]; sociodemographic characteristics and illness history were collected, intensity of mania was assessed by the Mania State Rating Scale (MSRS) [2, 15]; depression using the Montgomery Åsberg Depression Rating Scale (MADRS) [36, 38] and a newly derived depression checklist least contamined by mania [3]; psychotic symptoms were recorded on the Scale for Assessment of Positive Symptoms (SAPS) [8, 18], whereas mood disturbances were self reported by assessing the Multiple Visual Analog Scales of Bipolarity (MVAS-BP) [1, 5].

Alcohol and other substance use was globally defined as "excessive" when it was continued for 1 month in the year preceding mania onset despite social, occupational or psychological problems associated with the substance; it was judged as "moderate" in other cases; and "no use" when absent.

After marked improvement of the manic episode, on average 21 days from admission, self-reporting of affective temperament (hyperthymic, depressive, cyclothymic and irritable) with four questionnaires were filled out by the patient [25]; also stressful life events during the 3 months before the original onset of illness were reconstructed as far as possible on the basis of interviews with patients and their families and hospital records, following the guidelines for assessment of the DSM-IV Axis-IV [7].

Patients and their families were also asked about regular intake of treatment during the 6 months preceding the current episode.

Finally, the Social and Occupational Functioning Assessment Scale (SOFAS) [7] was used to evaluate functioning for the past year.

Most scales were used in their respective French versions, as validated in our prior EPIMAN Study [6, 10]. As far as the MADRS, SAPS and SOFAS scales, they had been validated by others as noted above.

The study was reviewed by the appropriate ethics committee and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. All patients gave informed consent prior to their inclusion in the study.

Statistical analyses

Subtyping of patients in distinct groups was based on cluster analysis using the SAS® CLUSTER procedure [20].

This procedure consists in a hierarchical clustering technique in which at each particular stage of the process the two groups of individuals which are the closest (or more similar) are fused into a single cluster. The distance between two clusters was computed using the Ward's minimum-variance method [46].

The number of clusters was determined on the basis of the cubic clustering criteria (CCC), the pseudo F statistic (PSF) and the t^2 statistic (PST2).

Nineteen variables which characterized the history of bipolar disorder and the symptoms of current episode, were initially retained from the baseline assessment of patients: age at onset, duration of the disease (delay from symptom onset to current episode), lifetime number of previous mood episodes, lifetime suicide attempts (at least one), alcohol use, other substance use, mania severity according to DSM-IV criteria, MSRS total score, MVAS-BP total score, SOFAS total score, dysphoria, number of depressive symptoms, MADRS total score, SAPS total score, SAPS Hallucination subscore, SAPS Delusion subscore, SAPS Bizarre behavior subscore, SAPS Positive formal thoughts subscore and SAPS Hallucination or Delusion subscore ≥3. Correlated variables were identified using the SAS® CORR procedure [20]. Groups of noncorrelated variables were tested with the cluster procedure. The squared multiple correlation R^2, was used to choose the group of variables retained in the model of best fit. Variables finally selected were: alcohol use, other substance use, duration of the disease (delay from symptom onset to current episode), lifetime suicide attempts (at least one), and SAPS Hallucination or Delusion subscore ≥3.

To evaluate the validity of the clusters, the groups were compared on sociodemographic, illness course, symptomatic and psychometric characteristics by using Chi-square or Fisher exact test (categorical variables) and ANOVA (continuous variables). The adjusted P value after Bonferroni-type correction was set at $P = 0.001$.

Results

Sample composition and population characteristics

We exceeded our goal of 1,000 French manic patients and actually recruited a total of 1,090 patients, 21.9% were categorized as mild or moderate, 78.1% as severe, whereas 4% fulfilled the criteria for mixed episode, according to DSM-IV criteria. All were bipolar I patients who had experienced manic plus depressive episodes (Bipolar I Disorder, Most Recent Episode Manic or Mixed, according to DSM-IV), to the exception of 82 patients who experienced their first episode of illness (Bipolar I Disorder, Single Manic or Mixed Episode), at inclusion (Table 3). Mean current age was 43 (±14) years. Fifty-eight percent were female. The proportion of married patients was 37.8%, 37.9 were single, and 24.3% divorced or widowed. The mean number of prior episodes was 7.2 (±8), with multiple hospitalizations in 66.1% and rapid cycling in 9%. The mean delay between symptom onset and

Table 1 Characteristics of four mania subtypes identified using cluster analysis in 1,090 patients included in EPIMAN-II Mille

	Classic mania (n = 318)	Psychotic mania (n = 248)	Depressive mania (n = 332)	Dual mania (n = 192)
Percentage of patients	29.3	22.7	30.4	17.6
Alcohol use (%)				
No use	48.7	56.3	53.5	23.7
Moderate	44.3	40.0	39.8	63.7
Excessive	7.0	3.7	6.7	12.6
Other substance use (%)				
No use	100.0	98.8	94.5	0
Moderate	0	1.2	5.5	81.1
Excessive	0	0	0	18.9
Delay (year), mean (SD)				
Symptom onset-current episode	14.72(12.03)	13.23(10.76)	18.75(11.29)	7.88(8.68)
Suicide attempts, n (%)	0	0	100.0	24.7
At least one in lifetime				
Psychotic symptoms	0	100.0	36.2	40.5
SAPS hallucination or delusion subscore ≥3(%)				

SAPS scale for the assessment of positive symptoms

Table 2 Demographic characteristics of 1,090 patients in the four subtypes "classic mania", "psychotic mania", "depressive mania" and "dual mania" identified using cluster analysis

	Classic mania (n = 318)	Psychotic mania (n = 248)	Depressive mania (n = 332)	Dual mania (n = 192)	Unadjusted P value
Age (year), mean (SD)	45.95 (13.66)	43.46 (13.24)	45.87 (12.02)	31.55 (11.29)	<0.0001
Gender (female) (%)	57.9	61.6	65.7	38.4	<0.0001
Marital status (%)					
Single	28.5	35.1	32.2	67.4	<0.0001
Married	47.2	40.8	36.2	20.5	
Divorced, widowed	24.4	24.1	31.6	12.1	

current episode was 14.43 (±11.57) years. Thirty-five percent attempted suicide at least once. Excessive alcohol use was recorded in 7.2% and excessive use of other substances in 3.3%.

Cluster analysis

Cluster analysis identified four subtypes underlying acute mania (Table 1). The first cluster (n = 318) was characterized by low rates of substance use, suicide attempts and psychotic symptoms. The second (n = 248) included patients with a low level of substance use, no lifetime suicide attempts, but psychotic symptoms. The third cluster (n = 332) was described by the presence of suicide attempts and a longer delay between symptom onset and current episode. The fourth cluster (n = 192) had a high proportion of substance use with shorter delay between symptom onset and current episode. These clusters will be labelled "classic mania", "psychotic mania", "depressive mania" and "dual mania".

Demographic characteristics of mania clusters

Table 2 summarizes sociodemographic features of the four clusters. Patients in the dual group were significantly younger than in other groups, whereas patients in the psychotic group were younger than in the classic and depressive mania clusters. Males were significantly overrepresented in the dual group. Singles were more represented in the dual cluster, married in the classic cluster, and divorced or widowed in the depressive cluster.

Characteristics of illness course in mania clusters

Characteristics of illness course for the four clusters are summarized in Table 3. Patients in the dual cluster had an earlier age of onset compared to the other groups, whereas patients in the depressive cluster had an earlier age at onset compared to those in the classic and psychotic clusters; the same trend was observed for age at first hospitalization.

Presence of episodes without free intervals was more often found in the depressive cluster. First episode patients were overrepresented in the dual cluster.

Clusters differed in regard to polarity of first episode: mania was predominant in the dual cluster, whereas patients in the depressive cluster had more depressive or mixed first episodes compared to the other groups.

Table 3 Illness course characteristics of 1,090 patients in the four subtypes "classic mania", "psychotic mania", "depressive mania" and "dual mania" identified using cluster analysis

	Classic mania (n = 318)	Psychotic mania (n = 248)	Depressive mania (n = 332)	Dual mania (n = 192)	Unadjusted P value
Age (year) at onset, mean (SD)	31.23 (11.51)	30.23 (11.36)	27.12 (9.52)	23.67 (8.20)	<0.0001
Age (year) first hospitalzation, mean (SD)	34.31 (12.12)	33.16 (12.05)	29.85 (10.38)	25.72 (9.36)	<0.0001
Illness progression (%)					
Slow	3.2	2.0	2.4	2.6	<0.0001
Episodes with Free intervals	72.8	69.4	62.6	57.4	
Episodes without Free intervals	17.4	21.6	32.8	21.1	
First episode	6.6	6.9	2.1	18.9	
First episode polarity (%)					
Mania	52.7	58.4	37.1	70.5	<0.0001
Depression	36.2	27.8	46.5	20.5	
Mixed	11.1	13.9	16.4	8.9	
N previous episodes, mean (SD)	7.07 (9.61)	6.10 (6.19)	9.4 (8.64)	4.97 (6.23)	<0.0001
Rapid cycling (%)	9.9	5.2	10.7	9.6	0.15
Prior diagnosis (%)					
Psychotic disorder	13.7	28.4	24.1	20.5	0.0002
Anxiety disorder	19.7	14.8	23.5	10.0	0.0006
Major depressive disorder	14.6	10.3	17.4	9.5	0.02
Personality disorder	26.0	24.5	35.4	26.5	0.04
Substance abuse	5.4	4.5	7.6	29.8	<0.0001
Mostly reported stressors (illness onset) (%)					
Divorce/separation	13.9	14.7	23.4	15.1	<0.0001
Immigration	5.4	13	6.3	6.1	<0.0001
Substance use	0.6	1.6	3.3	31.6	<0.0001

Patients in the depressive cluster showed a higher number of episodes compared to the other groups. Clusters did not differ in regard to rapid cycling, although the psychotic cluster included numerically less rapid cyclers.

Before receiving the DSM-IV diagnosis of bipolar I disorder, patients were more often diagnosed as having anxiety, major depressive or personality disorder in the depressive cluster, psychotic disorder in the psychotic cluster, and substance abuse disorder in the dual cluster.

Divorce/separation was a stressful life event which was more often found at the onset of depressive mania, immigration at the onset of psychotic mania and substance use at the onset of dual mania.

Clinical and psychometric characteristics of mania clusters

Patients in the depressive cluster had more depressive symptoms and more severe depression compared to the other groups.

The severity of mania was higher in the psychotic and dual mania clusters. Patients in the classic group were characterized by higher scores for the MSRS euphoria and the MVAS-BP anxiety–depression component (which means low anxiety–depression, confirmed by lower scores for the MSRS depression component). The psychotic cluster had higher scores for the MSRS psychosis component. The depressive cluster showed higher scores for the MSRS depression component and lower scores for the MVAS-BP anxiety–depression component. The dual cluster had higher scores for the MSRS disinhibition, hostility, and deficit and hypersexuality components and for the MVAS-BP expansiveness, risk-taking, psychomotor acceleration, social disinhibition, sleep, and anger components.

SOFAS scores were lower in the psychotic and dual clusters. Higher scores for hyperthymic temperament were found in the dual cluster, whereas higher scores for depressive temperament were found in the depressive cluster. The depressive and dual cluster had higher scores for both cyclothymic and irritable temperaments. The dual cluster had the lowest proportion of patients who regularly took their treatment (Table 4)

Discussion

General findings

The five variables which were selected by cluster analysis as the most cogent to subtype mania were alcohol use, other substance use, delay from symptom onset to current episode, lifetime suicide attempts and presence of psychotic symptoms (R^2 = 0,443). Four clusters were identified: classic mania, psychotic mania, depressive mania and dual mania.

To the best of our knowledge four other cluster analytic studies of mania have already been published

Table 4 Clinical and psychometric characteristics of 1,090 patients in the four subtypes "classic mania", "psychotic mania", "depressive mania" and "dual mania" identified using cluster analysis

	Classic mania (n = 318)	Psychotic mania (n = 248)	Depressive mania (n = 332)	Dual mania (n = 192)	Unadjusted P value
≥2 Depressive symptoms (%)	26.3	25.3	41	24.7	<0.0001
MADRS total score, mean (SD)	14.08 (6.56)	14.93 (7.03)	16.99 (8.16)	14.99 (6.76)	0.0002
MSRS total score, mean(SD)	186.76 (66.08)	237.82 (68.53)	209.61 (73.43)	231(77.14)	<0.0001
MSRS component scores, mean (SD)					
Disinhibition	83.50 (29.36)	89.59 (26.07)	85.64 (26.51)	91.10 (27.47)	0.009
Hostility	24.35 (18.05)	30.04 (23.31)	29.27 (21.48)	33.32 (23.88)	<0.0001
Deficit	23.42 (15.17)	30.76 (17.04)	27.31 (16.26)	32.76 (17.04)	<0.0001
Psychosis	14.80 (11.02)	35.70 (16.17)	22.22 (16.23)	28.24 (16.65)	<0.0001
Euphoria	22.87 (11.44)	20.31 (11.14)	18.68 (11.21)	19.29 (10.85)	0.0004
Depression	14.40 (9.34)	15.38 (8.92)	17.87 (11.41)	16.57 (9.43)	0.001
Hypersexuality	8.33 (8.38)	8.63 (9.94)	7.00 (11.12)	10.03 (10.07)	<0.0001
MVAS-BP component scores, mean(SD)					
Expansiveness	389 (104.19)	411.9 (92.76)	378.16 (107.54)	420.72 (86.33)	<0.0001
Risk taking	570.64 (124.05)	600.61(114.98)	565.31 (131.57)	615.36 (106.53)	<0.0001
Psychomotor acceleration	285.39 (68.14)	293.74 (67.82)	277.77 (70.80)	299.40 (64.98)	0.0001
Anxiety-depression	182.84 (71.33)	176.46 (71.88)	158.43 (76.23)	170.68 (7025)	0.001
Social disinhibition	198.91 (61.72)	197.03 (66.42)	186.04 (64.08)	204.79 (58.77)	0.01
Sleep	60.75 (29.56)	63.10 (28.01)	64.35 (30.05)	69.07 (27.81)	0.01
Anger	47.14 (31.92)	48.47 (33.34)	49.04 (32.29)	52.24 (32.62)	0.001
SOFAS, total score, mean(SD)	59.35 (7.11)	47.01 (9.13)	52.11(8.25)	46.71 (8.64)	<0.0001
Affective temperaments, dimensional measures, mean(SD)					
Hyperthymic	13.43 (5.05)	12.22 (4.83)	12.62 (4.85)	14.04 (4.42)	0.001
Depressive	7.52 (3.74)	7.73 (4.07)	11.42 (4.11)	7.12 (3.94)	<0.0001
Cyclothymic	9.73 (5.27)	9.74 (5.13)	11.33 (5.01)	10.95 (5.60)	<0.0001
Irritable	5.54 (3.95)	5.93 (3.89)	6.84 (4.25)	7.78 (4.66)	<0.0001
Regular intake of treatment in previous 6 months (%)	57.6	47.4	60.9	36.4	<0.0001

MADRS Montgomery Åsberg Depression Rating Scale
MSRS Mania State Rating Scale
MVAS-BP Multiple Visual Analog Scales of Bipolarity
SOFAS Social and Occupational Functioning Assessment Scale

[21, 27, 42, 45]. Four clusters were obtained in two studies [42, 45], only three in one [27] and two in the last [21]. Classic (also called "pure" or "typical" mania), as well as psychotic mania, were identified in all studies. Depressive (or "mixed") mania was obtained in three previous analyses [21, 42, 45]. Dual mania was found in one of these studies [27]. A cluster labelled "irritable" or "aggressive" that was identified in two studies [42, 45] shares some clinical characteristics with our "dual" subtype. Differences found between studies may be related to the characteristics of the population included and to the nature of variables available for analysis. For example, in both EMBLEM and EPIMAN-II Mille, cluster analysis was not based solely, as in the three other studies [21, 42, 45], on mere factor scores following a principal component analysis of a rating scale, but on a series of clinical and illness course characteristics. EMBLEM population included both in- and out-patients from several European countries, whereas EPIMAN-II Mille was a French national multisite study conducted on manic patients during their hospitalization. In the study by Sato et al. [42], all patients were hospitalized in only one center in Germany. Finally, the population of Swann et al. [45] consisted of patients participating in a clinical trial, so that severe patients as well as patients with substance abuse may have been excluded. Manic patients in the Dilsaver et al. study [21] were all hospitalized in one center in the US.

Delineating mania subtypes

Despite such differences, many similarities deserve further attention. We found rates of 29.3% for *classic mania* which is about 10–30% below the percentage found in previous analyses. It is likely, as will be shown, that many patients included in the classic group in previous studies may belong to our dual group. The EMBLEM study [27] which showed the highest percentage (59.1%) of "typical" manics also failed to identify a "depressive" cluster due to an insufficient assessment of depressive variables, so that many patients labelled "typical" in this study may have been "depressive" manics.

In accordance with previous studies our "classic" cluster included patients with less severe mania characterized by high euphoria scores, free intervals during episodes, as well as better adaptation to both marital and social life. Previous findings of high levels of hyperthymic temperamental traits conferring protection against depressive symptom formation during a manic episode [6] were confirmed in this group.

The percentage of 22.7% found in the *psychotic mania* is in the same range as that of previous cluster analytic approaches [27, 42, 45]. In line with those and other studies [12], patients in this group were characterized by the presence of severe mania, younger age (compared to classic and depressive mania), social impairment and low rapid cycling. Psychosis, as previously reported [37], was not associated with suicide attempts. The most frequent prior diagnosis before identification of bipolar disorder was that of psychotic disorder. Immigration was found to be the most frequently reported stressor preceding illness onset: this can be interpreted as reflecting ethnic differences [32], social isolation consecutive to migration [12] or high levels of stress during the interval between the uprooting and the outbreak of the symptoms, precipitating bipolar disorder in vulnerable subjects [40].

The *depressive mania* cluster showed rates of 30.4%, which corresponds to the overall mean rates of 31% found by McElroy et al. [35] for dysphoric mania, despite the wide variation in definition and rates across studies. We found, in accordance with most studies [21, 26, 34, 42, 45], that depressive manics were characterized by: female gender, high levels of divorced/widowed, high number of previous episodes and suicide attempts, presence of episodes without free intervals, high levels of anxiety and depression, associated depressive symptoms, severe social impairment (compared to classic mania), depressive or mixed first episode polarity and prior diagnoses of anxiety, major depressive or personality disorder. High levels of depressive, cyclothymic and irritable temperamental traits confirmed previous findings [6]. High rates of divorce/separation were found preceding illness onset. As subthreshold levels of depressive features have been associated with social impairment in bipolar patients [29], we submit that presence of depressive, cyclothymic or irritable traits may favor marital disruption and subsequently trigger illness onset.

Our data confirm previous findings of a *dual mania cluster* by Haro et al. [27] with approximately comparable rates of 17.6% (vs. 13% in the Haro study). Similar to the results of the EMBLEM study, we found that dual mania was associated with male gender, younger age, single status, earlier age at onset, risk of suicide attempts in one-fourth of patients, severe social impairment, and poor compliance.

About one-fifth of the patients presented as first episode, and first episode polarity was predominantly manic. The most frequent previous diagnosis before identification of bipolar disorder was substance abuse followed by personality disorder. These patients exhibited severe mania characterised by high levels of disinhibition, hostility, hypersexuality, expansiveness, risk taking, psychomotor acceleration, anger and deficit. This clinical profile is close to that of "irritable" or "aggressive" mania found in other cluster analyses [42, 45]. They showed the highest levels of hyperthymic temperamental traits, which may be related to the high rates of male gender [6]. They also scored high on measures of both cyclothymic and irritable temperaments. Illness onset was found to be preceded by substance use in 31.6% of the cases. It is possible in these cases that, as previously evidenced [4], hyperthymic or cyclothymic temperamental traits may favor risky behaviors such as substance abuse which may trigger disease onset in genetically predisposed individuals. This is in accordance with data from recent studies [24] showing that, in dual patients, about one-fourth had a chronologically "primary" substance use disorder. More provocatively, Winokur et al. [47] hypothesized the existence of a mania subtype that shares familial genetic basis with stimulant abuse.

Limitations

These are roughly those of previous cluster analytic approaches. First, random distribution of available variables might have produced apparent clusters of patients. However, the relative homogeneity of clusters identified across different studies, using not always the same variables, argues against the lack of relevance of patient subtyping.

Second, the EPIMAN-II Mille population did not include manic outpatients, limiting the generalizability of our findings to the most severe patients. However, our findings are close to those of Swann et al. [45] who included less severe patients (those participating in a clinical trial) and to those of the EMBLEM study [27] in which 60.5% were outpatients. Third, no information about bipolar II was provided. However this was linked to the design of the study which focused on mania and therefore included bipolar I patients only, based on DSM-IV criteria. Fourth, 317 psychiatrists working at 19 medical centers in France participated as investigators, which may have reduced the reliability of evaluations. However all these investigators had considerable experience in studies and instruments used with bipolar patients.

Finally, some data, such as those concerning stressors preceding illness onset, were retrospectively collected and therefore submitted to recall bias. However these data were gathered using different sources of information.

Clinical and genetic implications

First, unless mania is properly subtyped, bipolar disorder may be misdiagnosed. Second, there is evidence that the four subtypes may exhibit different responses to pharmacologic treatment: lithium seems to have better efficacy in classic mania than in the other groups [17]; patients from the psychotic cluster may better respond to atypical antipsychotics (±mood

stabilizer) [30], anticonvulsants and atypicals are probably more appropriate for depressive mania [44] and, finally, several studies further indicate that anticonvulsants may be efficacious in dual mania [41, 43]. Third, risks associated with the illness such as suicide attempts, residual symptoms, relapses, marital disruption, social impairment or poor compliance are differently shared by the four subtypes.

For everyday clinical use, the latter should be easily defined on the basis of a few variables such as age, gender, psychosis, depression, euphoria and substance use; that may help clinicians to correctly recognize the four subtypes, so to select the most efficient drug treatment and take the best appropriate measures to prevent the corresponding risks. Differential pharmacologic response in different mania subtypes may ultimately help identify specific manic "phenotypes" suitable for genotyping [3, 9, 31, 47].

Acknowledgments Funding source: supported by a grant from Sanofi-Aventis, France

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