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Original article

Baseline and prodromal characteristics of first- versus multiple-episode mania in a French cohort of bipolar patients

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ABSTRACT

Objective: To identify some of the main features of bipolar disorder for both first-episode (FE) mania and the preceding prodromal phase, in order to increase earlier recognition.
Methods: One thousand and ninety manic patients (FE = 81, multiple-episodes [ME] = 1009) were assessed for clinical and temperamental characteristics.
Results: Compared to ME, FE patients reported more psychotic and less depressive symptoms but were comparable with respect to temperamental measures and comorbid anxiety. The following independent variables were associated with FE mania: a shorter delay before correct diagnosis, greater substance use, being not divorced, greater stressors before current mania, a prior diagnosis of an anxiety disorder, lower levels of depression during index manic episode, and more suicide attempts in the past year.
Conclusion: In FE patients, the diagnosis of mania may be overlooked, as they present with more psychotic symptoms than ME patients. The prodromal phase is characterised by high levels of stress, suicide attempts, anxiety disorders and alcohol or substance abuse. Data suggest to consider these prodromes as harmful consequences of temperamental predispositions to bipolar disorder that may concur to precipitate mania onset. Their occurrence should therefore incite clinicians to screen for the presence of such predispositions, in order to identify patients at risk of FE mania.

1. Introduction

Observational studies comparing bipolar patients experiencing their first-episode (FE) of mania to those who have experienced multiple-episodes (ME) of mania have suggested a better outcome in FE patients, with more rapid recovery and remission [37,55–59]. In line with this finding, it was hypothesised that the activation of neurotransmitter pathways during an initial episode of mania could induce permanent neuronal alterations, causing additional episodes to be more easily triggered and to last longer [50]. The best study design to assess the impact of manic recurrences on the patient profile and illness characteristics would likely be one that follows FE patients longitudinally. However, such prospective studies are difficult to conduct, mainly due to the low incidence of mania and high rates of attrition [39]. As a whole, FE mania has been relatively understudied, especially compared to the growing interest devoted to the early phase of psychosis, and despite the awareness that the key principles of early intervention for individuals with psychosis may apply equally well to individuals with bipolar disorder [19,20].

Studies conducted in populations of bipolar offspring may provide valuable information concerning the progress of the disease; however, this information is only relevant to subjects for whom genetic factors play a role in the development of bipolar disorder [21]. It was therefore recently recommended that, in addition to prospective studies in high-risk groups, retrospective surveys in FE manic cohorts be implemented, which would focus on the few months preceding FE mania. The latter might help identify prodromes that could become a new target for early intervention [20].

Conclusions drawn from studies conducted to date in both FE and ME manic patients have been limited due to small sample sizes resulting in poor statistical power [37,55–59]. The Epidemiology of Mania (EPIMAN) II-Mille Study represents one of the largest observational studies conducted with patients suffering from bipolar mania. This large-scale study offers a unique opportunity to examine and compare FE and ME manic patients within the same sample base population. The aims of the current work were as follows:

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1) to identify differences between FE and ME manic patients in baseline clinical features;
2) to characterise the prodromal phase for FE mania;
3) to try to understand the transition from the former to the latter;
4) to find out, early in the course, identifying features of bipolar disorder.

2. Material and methods

2.1. Study population

Patients included in the study were patients from both sexes, between the ages of 18 and 65 years, and hospitalised for a manic or mixed episode occurring in the context of a primary bipolar I disorder. Manic or mixed episodes occurring in the context of schizoaffective disorder were excluded; were also excluded patients for whom manic or mixed episodes were due to the direct physiological effects of a substance or a general medical condition. Diagnosis was made using the French version of the Structured Clinical Interview for DSM-IV (SCID) [15,26].

2.2. Study design

EPIMAN II Mille, implemented in France, was a multicenter, naturalistic study conducted at 19 medical centres between December 2000 and April 2002. The primary aim of the study was to further characterise the validity of the different subtypes of mania and to estimate their prevalence in this national clinical sample. Our objective was to enroll 1000 patients. To reach this goal, each of the 317 psychiatrists had to recruit consecutively at least two manic or mixed patients (with a maximum of six patients recruited by each psychiatrist). All psychiatrists working in public, university, or private hospitals had considerable clinical experience with studies involving bipolar disorder patients. This study exceeded the initial target of 1000 patients with the final inclusion of 1090 patients. This large sample size gave us the opportunity to compare the characteristics of FE and ME patients, both at baseline and during the year preceding study entry.

2.3. Clinical assessments

During the screening phase, sociodemographic characteristics and illness history data were collected. FE was defined as the first occurrence of a manic or mixed episode. ME was defined as the occurrence of at least two manic or mixed episodes in the patient's lifetime, including the current episode. Hence, patients with a previous depressive episode who were experiencing their first manic or mixed episode were considered FE patients.

Alcohol and other substance use was defined as "excessive" when it was continued for greater than one month in the year preceding the onset of the current mania episode and the substance use caused social, occupational or psychological problems; it was defined as "moderate" in all other cases of use; and it was defined as "no use" when absent. Intensity of mania was assessed by the Mania State Rating Scale (MSRS) [1,14], and depression during the manic episode was assessed using the Montgomery Åsberg Depression Rating Scale (MADRS) [46,47].

Delay before correct diagnosis of bipolar I disorder and delay to first mood stabiliser treatment were retrospectively assessed for both FE and ME patients on the basis of patient and family interviews and hospital records. Delay before correct diagnosis was measured by the percentage of patients receiving correct diagnosis after at least 5 years from their first seeking help. The illness onset was defined when the first symptoms met the Research Diagnostic Criteria for an affective episode [52].

After marked improvement of the manic episode, on average 21 days from admission, patients self-reported their affective temperaments using four different questionnaires (i.e., hyperthymic, depressive, cyclothymic and irritable) [31]. Lifetime comorbid anxiety was assessed using the SCID probes. Stressful life events during the three months prior to the onset of the current manic episode were reconstructed as much as possible using patient and family interviews and hospital records, as suggested by the DSM-IV Axis-IV assessment guidelines [7]. A recording form with a checklist was used, in which stressors were grouped together in the following categories: problems with primary support group, problems related to the social environment, educational problems, occupational problems, housing problems, economic problems, problems with access to health care services, problems related to interaction with the legal system/crime and other psychosocial and environmental problems. So-called positive stressors, such as job promotion, were listed only if they constituted or led to a problem. Most scales were used in their respective French versions, as validated in our prior EPIMAN study [10]. The MADRS has been validated by other researchers, as noted above. The study was reviewed and approved by the appropriate ethics committee, and patients participated with informed, voluntary, written consent.

2.4. Statistical methods

For categorical variables, we used χ^2 or Fisher's exact test for comparisons between groups. For continuous variables with normal distribution, we used a two-sample *t*-test for comparison between groups; where assumptions of normality were not adequately met, differences between groups were tested using the Mann-Whitney test.

Stepwise logistic regression models were then used to correct for possible confounding variables. Those variables associated with the FE (versus ME) group at at least $P \leq 0.2$ on univariate analyses were entered into the model as independent variables. Odds ratios with 95% confidence intervals were used for observed associations.

3. Results

One thousand and ninety bipolar I manic patients were included in the analyses. Of those, 81 (7.4%) were currently experiencing their first episode of mania whereas 1,009 had multiple-episode mania. Among the latter, 74% had already been given a diagnosis of bipolar I prior to study entry. The mean age of the study population was 42.92 ± 13.74 years; 57.7% were female. Mixed episodes were recorded in 44 patients.

3.1. Univariate analysis

3.1.1. Demographic and clinical characteristics

FE patients were younger than ME patients ($P < 0.0001$) (Table 1). A trend was observed for women to be overrepresented in ME ($P = .07$). FE and ME patients differed in marital status, which was mainly due to an overrepresentation of single patients in FE and divorced patients in ME ($P < 0.0001$). Compared to ME, FE patients scored higher on the MSRS component measures of psychosis ($P = 0.02$) and euphoria ($P = 0.01$), but scored lower on the depression MSRS component ($P = 0.02$) and MADRS total ($P = 0.01$) scores. The two groups did not significantly differ in regard to rates of mixed episodes according to DSM-IV criteria, MSRS total scores and affective temperaments.

3.1.2. Illness course and comorbidity

In comparison to ME, FE patients had shorter delays before both correct diagnosis ($P < 0.0001$) and their first mood stabiliser