

On the prevalence of bipolar disorder in epilepsy

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ABSTRACT

Although mood disorders represent a frequent psychiatric comorbidity in epilepsy, data on bipolar disorder (BD) are still limited, and the role of possible specific confounding variables (seizures and antiepileptic drug therapy) has never been considered. Data for 143 adult outpatients with epilepsy assessed with the Mini International Neuropsychiatric Interview Plus Version 5.0.0 using the Epilepsy Addendum for Psychiatric Assessment, the Mood Disorder Questionnaire, and the Interictal Dysphoric Disorder Inventory revealed that 11.8% had the *Diagnostic and Statistical Manual of Mental Disorders*-based diagnosis of BD, only 1.4% of whom could be considered as having “pure” BD, because in all other cases BD symptoms were related to phenotype copies of BD such as interictal dysphoric disorder of epilepsy, postictal manic or hypomanic states, and preictal dysphoria.

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1. Introduction

Mood disorders represent an often-encountered psychiatric comorbidity among patients with epilepsy [1,2]; however, the majority of studies have focused on major depression, with information about bipolar disorder (BD) still being limited.

Bipolar disorder is a severe mental illness associated with considerable mortality and morbidity. It is currently classified, within the framework of the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV) [3], as bipolar I disorder (mania and depression) and bipolar II disorder (hypomania and depression). Epidemiological studies suggest that BD affects between 1 and 2% of the general population [4,5], although several authors point out that bipolarity is still largely underdiagnosed [6,7]. Thus, in an attempt to improve its recognition, self-report instruments such as the Mood Disorder Questionnaire (MDQ) [8] have been developed to screen clinical and nonclinical samples for mania/hypomania symptoms. On this background, the importance of clarifying whether this psychiatric comorbidity occurs in patients with epilepsy is obvious, because specific treatment strategies would be needed and the prognosis of the epilepsy may be significantly modified by the presence of such comorbidity.

In the older literature, it was often stated that BD was rare in patients with epilepsy [9]. However, such a statement was made prior to the use of standardized diagnostic manuals such as the DSM-IV, and was based on clinical impressions rather than on systematic assessments. On the contrary, a large U.S. survey [10] revealed that 12.2% of patients with epilepsy screened positively, with the MDQ, for bipolar symptoms (BS), a rate twice that of people with asthma and seven times that of a healthy comparison group. Of those who, in the screening process, were rated as potential patients with BS, nearly half (6%) were rated by a physician as having a BD.

These data challenge the previous belief that BD is rare in people with epilepsy, and raise doubts as to our understanding of the association between these two disorders. However, several points need to be further elucidated. The first is whether it is classic manic–depressive illness that is frequent in epilepsy or other clinical entities such as interictal dysphoric disorder (IDD) [11] that is misdiagnosed as BD. Moreover, the number of behavioral changes that may occur around the ictus need to be taken into account [12]. Finally, manic symptoms may occur, although rarely, as side effects of antiepileptic drug (AED) therapy [13]. All these issues need to be carefully considered because they may have several implications in terms of diagnosis, prognosis, and treatment strategies. Thus, this study was aimed at describing the prevalence of BD and BS in a population of patients with epilepsy, taking into special account relationships between psychiatric symptoms and seizures or drug therapy.

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2. Methods

2.1. Study sample

For this descriptive study, adult outpatients with epilepsy were recruited in two tertiary referral centers in Europe, namely, the Department of Neurology, Amedeo Avogadro University, Novara, Italy, and the Department of Neurology, Universitätsmedizin-Charité, Berlin, Germany. To be enrolled, patients had to fulfill the following criteria: (1) diagnosis of epilepsy according to ILAE criteria [14]; (2) age greater than 18; (3) absence of learning disabilities, a reading level higher than sixth grade, and/or a Mini Mental State Examination score >24; (4) absence of severe medical diseases or a high risk of suicide when assessed (these are widely accepted exclusion criteria in psychiatric research); (5) willingness to provide a written informed consent to undergo the experimental procedures.

2.2. Assessment procedures

All subjects were assessed with the Mini International Neuropsychiatric Interview (MINI) Plus, Version 5.0.0 [15], using the Epilepsy Addendum for Psychiatric Assessment (EAPA) [16], the Mood Disorder Questionnaire (MDQ) [8], and the Interictal Dysphoric Disorder Inventory (IDDI) [17,18]. All interviews were conducted by research clinicians who were trained in the use of the study instruments under the supervision of a neuropsychiatrist trained in neurology and psychiatry (M.M., B.S.).

The MINI Plus 5.0.0 was developed from the MINI [15] as an efficient diagnostic interview to be used in clinical as well as research settings, following DSM-IV and ICD-10 criteria. The MINI screens for a number of Axis I diagnoses with brief suicidality and antisocial personality modules. It has been validated in the United States and Europe and is available in several languages. The EAPA is an instrument expressly designed for use with the MINI in patients with epilepsy and consists of a brief series of directed questions designed to elaborate on several areas in which diagnoses of behavioral disorders in epilepsy may be confounded, taking into consideration medication-induced and seizure-related psychiatric symptoms.

The MDQ is a validated self-report instrument that screens for the presence of a lifetime history of bipolar disorder. An individual is scored positive if 7 or more of the 13 symptom items are endorsed and a moderate or serious degree of functional impairment is reported. The MDQ has been demonstrated to be a useful screening instrument for BD with sound psychometric properties (internal consistency = 0.90; sensitivity = 0.73; specificity = 0.90).

The IDDI is a 38-item self-report questionnaire specifically created to investigate IDD. The eight key symptoms (depressive mood, anergia, pain, insomnia, fear, anxiety, paroxysmal irritability, alternating euphoric mood) are evaluated in the first 32 items in terms of presence, frequency, severity, and global impairment. The time interval explored is the preceding 12 months. The six questions in the Appendix concern the time course of the disorder and relationships of symptoms to seizures and therapy. As suggested by Blumer et al. [11], a definite diagnosis of IDD is defined by the presence of at least three symptoms of at least “moderate” or “severe” severity and causing “moderate” or “severe” distress.

Considering the descriptive nature of the present report, no relevant statistical analyses have been carried out. Demographic and clinical variables were explored to test homogeneity of the sample using χ^2 analysis or Fisher’s exact test for categorical variables and the independent-sample *t* test for continuous variables. The Statistical Package for Social Sciences was used (Version 12 for Windows, SPSS Inc. Chicago, IL, USA).

3. Results

Data on 143 consecutive adult outpatients (83 females) with epilepsy (mean age [SD] = 42.7 [14.4]) were analyzed. Clinical and demographic data are summarized in Table 1. No patients were excluded because of high risk of suicide. Seventeen (11.9%) patients were diagnosed with BD according to DSM-IV criteria, whereas 21 (14.7%) patients screened positively for BS with the MDQ (16 of 17 with a MINI-based diagnosis of BD screened positively with the MDQ).

As far as AED therapy is concerned, 41.3% of patients were taking carbamazepine, 28% valproate, 19.6% lamotrigine, 16.8% levetiracetam, 11.2% topiramate, 9.8% barbiturates, 7.7% oxcarbazepine, and 0.7% phenytoin. The majority of patients (64.3%) were receiving monotherapy, 24.5% were on dual therapy, and 9.1% were on a polytherapy regimen with three or more anticonvulsants. As compared with patients treated with AEDs without mood-stabilizing properties, patients treated with at least one AED recognized as a mood stabilizer (i.e., carbamazepine, oxcarbazepine, lamotrigine, valproate) exhibited no difference in BD prevalence (15.2% vs 11.1%, $\chi^2 = 0.200$, *df* = 1, *P* = 1.000) or MDQ positive screening (13.3% vs 25%, $\chi^2 = 1.830$, *df* = 1, *P* = 0.184).

As shown in Fig. 1, among the 17 patients with a DSM-IV diagnosis of BD, 6 were diagnosed as having IDD, and in 9 patients, symptoms had a clear relationship with seizures or AED treatment. Therefore, the remaining number of subjects with “pure” BD was 2 (1.4%).

In the group of 21 subjects with a positive MDQ screening for BS, 9 were diagnosed with IDD, and among the remaining 12 patients, symptoms were clearly related to seizures or therapy in 9 cases, resulting in a total prevalence of 3 subjects (2%) who screened positively for “pure” BS.

4. Discussion

To the best of our knowledge, this is the first report on the prevalence of BD and BS in epilepsy looking specifically at differences from other clinical entities or the wide range of behavioral manifestations that may accompany seizures. Our data suggest that BS

Table 1
Demographic and clinical characteristics of the study sample (*N* = 143)

Gender	
Male	60 (42%)
Female	83 (58%)
Age, mean \pm SD	42.7 \pm 14.4
Epilepsy syndrome	
Cryptogenic partial	65 (45.5%)
Symptomatic partial	35 (24.5%)
Idiopathic generalized	32 (22.4%)
Symptomatic generalized	7 (4.9%)
Not otherwise specified	2 (1.4%)
Temporal lobe epilepsy	80 (55.9%)
Age at onset of epilepsy, mean \pm SD	22.9 \pm 18.1
Frequency of seizures	
Free	21 (14.7%)
<10/years	44 (30.8%)
1–10/month	60 (42.0%)
11–20/month	6 (4.2%)
>20/month	6 (4.2%)
AED therapy	
No therapy	3 (2.1%)
Monotherapy	92 (64.3%)
Dual therapy	35 (24.5%)
Polytherapy	13 (9.1%)
AED mood stabilizers (carbamazepine, valproate, oxcarbazepine, lamotrigine)	120 (83.9%)
MRI normal	93 (65.0%)

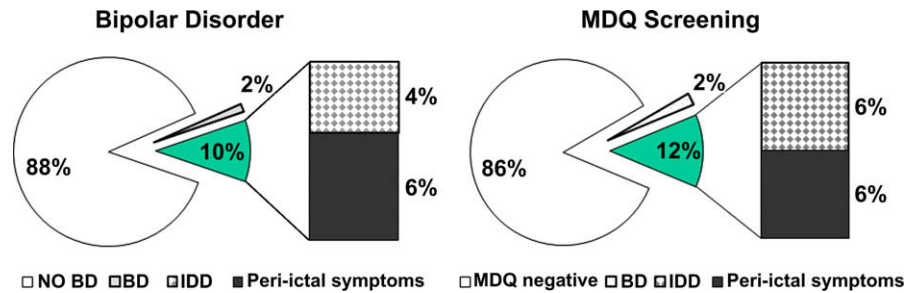


Fig. 1. Prevalence of DMS-IV-based diagnoses of bipolar disorder (BD) and Mood Disorder Questionnaire (MDQ) positive screening for bipolar symptoms in the total study sample. IDD, interictal dysphoric disorder.

frequently occur among patients with epilepsy, although, in the majority of cases, these symptoms are related to phenotype copies of BD, such as IDD, postictal manic or hypomanic states, and preictal dysphoria. In fact, the prevalence of true manic depressive illness in epilepsy has been demonstrated to be in line with that reported in the general population (about 2%) [4].

Several small series of patients with epilepsy and mania have been reported [19–22]. Manic symptoms have been described following temporal lobectomy, predominantly on the right side [23], or as treatment-emergent adverse effects of several AEDs [13].

In general terms, episodes of manic excitement can be seen more often in temporal lobe epilepsy than in other seizure types and may occur peri-ictally [24]. In fact, it was already accepted that, in the context of a postictal state, patients with epilepsy can develop a postictal psychosis, the features of which are often manic or hypomanic [25]. A Japanese study has shown that postictal mania has a distinct position among seizure-related psychiatric symptoms observed in epilepsy [26]. Postictal manic episodes may last for a longer period and may have a higher frequency of recurrence when compared with postictal psychoses. Moreover, postictal mania/hypomania seems to be associated with an older age at onset, EEG frontal discharges, and right hemisphere involvement [26]. Kanner et al. [27] described postictal manic/hypomanic symptoms in 22% of patients with drug-refractory epilepsy; in particular, 15% reported racing thoughts and 9% increased energy (both of these are considered DSM criteria for a manic episode). Symptoms were described as short-lasting (about 2 hours), but 6% of patients presented with hypomanic symptoms lasting 24 hours [28].

Although it has already been accepted that isolated manic/hypomanic symptoms could occur among patients with epilepsy, our study has pointed out that, in a not negligible proportion of patients, these symptoms are not isolated, fulfilling DSM criteria for a manic episode (at least three or more symptoms lasting at least a week), and may represent a diagnostic pitfall, not only for epileptologists, but also for psychiatrists not adequately trained in behavioral problems of patients with seizure disorders.

In the neuropsychiatry of epilepsy, the assessment of psychiatric symptoms is complicated by the number of behavioral manifestations that may occur around the ictus, and the lack of an accurate distinction between “true” psychiatric phenomenology and peri-ictal phenomena may lead to misinterpretations of symptoms. In a recent cross-sectional study in patients with epilepsy [17], we also overestimated BD diagnoses because, at that time, the psychopathological definition of IDD according to DSM criteria was the main purpose of the study, and the relationship between seizures and psychiatric symptoms was not analyzed. However, an accurate differentiation has practical implications in terms of treatment strategies for and prognosis of behavioral comorbidity in patients with epilepsy. In fact, it is evident that seizure control is important for all symptoms that

have a clear relationship to epileptic seizures, whereas widely accepted guidelines for treatment and prognosis of mental illnesses have to be used in cases where there is true psychiatric comorbidity.

Nonetheless, it must be acknowledged that, although BS related to BD in the strict sense differ considerably, all BS need to be recognized in studies of this area because the possible consequences can be profound regardless of the specific etiology. Severe manic or mixed episodes, especially if psychotic features are present, may have deleterious effects on social functioning and quality of life of patients with epilepsy whether they are postictal phenomena, are part of an IDD, or are due to true manic depressive illness. Moreover, suicide is strictly associated with BS [29], and although there is considerable variability in the reported rates of suicide in adults with epilepsy, there seems to be general agreement that the rate is significantly higher than in the general population [30]. It is thus evident that further studies clarifying relationships between BS and epilepsy may also be of value in shedding light on the issue of suicide in epilepsy, allowing the development of specific strategies for prevention and treatment.

Our findings need to be considered keeping in mind the following limitations. First, the small sample size reduces the epidemiological relevance of our data, also making it impossible to ensure comparisons, for relevant variables, between patients with true BD and other groups. However, this study represents a proof of principle and accurate psychiatric assessment, based on widely standardized clinical instruments, and the detailed clinical evaluation of the relationship between symptoms and seizures makes our results of interest. Second, our findings may not be representative of patients with epilepsy in general because our population represents a highly selected sample coming from tertiary referral centers. Studies in nonselected populations reported estimated prevalence rates of mental health disorders much lower than those reported in university-based clinics [31]. Third, information about relationships between psychiatric symptoms and seizures or AED therapy derived from patients’ reports and further studies objectively evaluating these associations with a longitudinal approach (e.g., seizure diaries and mood diaries) are needed to replicate our findings.

In conclusion, our preliminary results on the prevalence of BD in epilepsy open a number of issues that need to be addressed in future research. The first relates to the reasons why patients who are chronically taking potent mood stabilizers, such as AEDs, still have mood instability and BS. The second question relates to the relationship between mood instability and specific epilepsy syndromes and etiologies. Studies aimed at identifying clinical correlates of BD in epilepsy have theoretical relevance for the understanding of the neurobiology of mood disorders and may also shed light on the neurobiology of seizures that, so far, remain uncontrolled in a proportion of patients.

Conflict of interest statement

The authors of this paper do not have any commercial association that might pose a conflict of interest in connection with this article.

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References

- [1] Kanner AM. Depression in epilepsy: a frequently neglected multifaceted disorder. *Epilepsy Behav* 2003;4(Suppl. 4):11–9.
- [2] Marcangelo MJ, Ovsiew F. Psychiatric aspects of epilepsy. *Psychiatr Clin North Am* 2007;30:781–802.
- [3] Diagnostic and statistical manual of mental disorders—text revision. Fourth ed. Washington, DC: Am. Psychiatric Assoc; 2000.
- [4] Akiskal HS, Bourgeois ML, Angst J, Post R, Moller H, Hirschfeld R. Re-evaluating the prevalence of and diagnostic composition within the broad clinical spectrum of bipolar disorders. *J Affect Disord* 2000;59(Suppl. 1):S5–S30.
- [5] Judd LL, Akiskal HS. The prevalence and disability of bipolar spectrum disorders in the US population: re-analysis of the ECA database taking into account subthreshold cases. *J Affect Disord* 2003;73:123–31.
- [6] Lish JD, Dime-Meenan S, Whybrow PC, Price RA, Hirschfeld RMA. The National Depressive and Manic–Depressive Association (DMDA) survey of bipolar members. *J Affect Disord* 1994;31:281–94.
- [7] Thomas P. The many forms of bipolar disorder: a modern look at an old illness. *J Affect Disord* 2004;79(Suppl. 1):S3–8.
- [8] Hirschfeld RMA, Williams JBW, Spitzer RL, et al. Development and validation of a screening instrument for bipolar spectrum disorder: the mood disorder questionnaire. *Am J Psychiatry* 2000;157:1873–5.
- [9] Wolf P. Manic episodes in epilepsy. In: Akimoto H, Kazamatsuri H, Seino M, Ward Jr AA, editors. *Advances in epileptology: XIIIth Epilepsy International Symposium*. New York: Raven Press; 1982. p. 237–40.
- [10] Ettinger AB, Reed ML, Goldberg JF, Hirschfeld RM. Prevalence of bipolar symptoms in epilepsy vs other chronic health disorders. *Neurology* 2005;65:535–40.
- [11] Blumer D, Montouris G, Davies K. The interictal dysphoric disorder: recognition, pathogenesis, and treatment of the major psychiatric disorder of epilepsy. *Epilepsy Behav* 2004;5:826–40.
- [12] Trimble MR. The end of the seizure can be the beginning of the problem. *Neurology* 2004;62:683.
- [13] Mula M, Monaco F. Antiepileptic drug-induced mania in patients with epilepsy: what do we know? *Epilepsy Behav* 2006;9:265–7.
- [14] Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for a revised classification of epilepsies and epileptic syndromes. *Epilepsia* 1989;30:389–99.
- [15] Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry* 1998;59(Suppl. 20):22–33.
- [16] Mintzer S, Lopez F. Comorbidity of ictal fear and panic disorder. *Epilepsy Behav* 2002;3:330–7.
- [17] Mula M, Jauch R, Cavanna A, et al. Clinical and psychopathological definition of the interictal dysphoric disorder of epilepsy. *Epilepsia* 2008;49:650–6.
- [18] Mula M, Trimble MR. What we know about mood disorders in epilepsy. In: Kanner AM, Schachter S, editors. *Psychiatric controversies in epilepsy*. New York: Elsevier; in press.
- [19] Barczak P. Hypomania following complex partial seizures. *Br J Psychiatry* 1988;152:572.
- [20] O'Shea B. Hypomania following complex partial seizures. *Br J Psychiatry* 1988;152:571.
- [21] Robertson MM. Affect and mood in epilepsy: an overview with a focus on depression. *Acta Neurol Scand* 1992;86:127–35.
- [22] Kudo T, Ishida S, Kubota H, Yagi K. Manic episode in epilepsy and bipolar I disorder: a comparative analysis of 13 patients. *Epilepsia* 2001;42:1036–42.
- [23] Carran MA, Kohler CG, O'Connor MJ, Bilker WB, Sperling MR. Mania following temporal lobectomy. *Neurology* 2003;61:770–4.
- [24] Dunn DW, Austin JK. Psychiatric aspects of epilepsy in children. In: Schachter SC, Holmes GL, Kasteleijn-Nolst Trenité DGA, editors. *Behavioral aspects of epilepsy*. New York: Demos; 2008. p. 349–54.
- [25] Schmitz B. Depression and mania in patients with epilepsy. *Epilepsia* 2005;46(Suppl. 4):45–9.
- [26] Nishida T, Kudo T, Inoue Y, et al. Postictal mania versus postictal psychosis: differences in clinical features, epileptogenic zone, and brain functional changes during postictal period. *Epilepsia* 2006;47:2104–14.
- [27] Kanner AM, Soto A, Gross-Kanner H. Prevalence and clinical characteristics of postictal psychiatric symptoms in partial epilepsy. *Neurology* 2004;62:708–13.
- [28] Kanner AM. Postictal phenomena in epilepsy. In: Schachter SC, Holmes GL, Kasteleijn-Nolst Trenité DGA, editors. *Behavioral aspects of epilepsy*. New York: Demos; 2008. p. 105–16.
- [29] Akiskal HS, Benazzi F. Does the FDA proposed list of possible correlates of suicidality associated with antidepressants apply to an adult private practice population? *J Affect Disord* 2006;94:105–10.
- [30] Pompili M, Girardi P, Tatarelli G, Angeletti G, Tatarelli R. Suicide after surgical treatment in patients with epilepsy: a meta-analytic investigation. *Psychol Rep* 2006;98:323–38.
- [31] Tellez-Zenteno JF, Patten SB, Jetté N, Williams J, Wiebe S. Psychiatric comorbidity in epilepsy: a population-based analysis. *Epilepsia* 2007;48:2336–44.