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RESEARCH ARTICLE

Mood and Anxiety Disorders and Suicidality in Patients With Newly Diagnosed Focal Epilepsy

An Analysis of a Complex Comorbidity

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Abstract

Background and Objectives

Mood, anxiety disorders, and suicidality are more frequent in people with epilepsy than in the general population. Yet, their prevalence and the types of mood and anxiety disorders associated with suicidality at the time of the epilepsy diagnosis are not established. We sought to answer these questions in patients with newly diagnosed focal epilepsy and to assess their association with suicidal ideation and attempts.

Methods

The data were derived from the Human Epilepsy Project study. A total of 347 consecutive adults aged 18–60 years with newly diagnosed focal epilepsy were enrolled within 4 months of starting treatment. The types of mood and anxiety disorders were identified with the Mini International Neuropsychiatric Interview, whereas suicidal ideation (lifetime, current, active, and passive) and suicidal attempts (lifetime and current) were established with the Columbia Suicidality Severity Rating Scale (CSSRS). Statistical analyses included the *t* test, χ^2 statistics, and logistic regression analyses.

Results

A total of 151 (43.5%) patients had a psychiatric diagnosis; 134 (38.6%) met the criteria for a mood and/or anxiety disorder, and 75 (21.6%) reported suicidal ideation with or without attempts. Mood (23.6%) and anxiety (27.4%) disorders had comparable prevalence rates, whereas both disorders occurred together in 43 patients (12.4%). Major depressive disorders (MDDs) had a slightly higher prevalence than bipolar disorders (BPDs) (9.5% vs 6.9%, respectively). Explanatory variables of suicidality included MDD, BPD, panic disorders, and agoraphobia, with BPD and panic disorders being the strongest variables, particularly for active suicidal ideation and suicidal attempts.

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Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Glossary

ASM = antiseizure medication; **BPD** = bipolar disorder; **CSSRS** = Columbia Suicidality Severity Rating Scale; **MDD** = major depressive disorder; **MDE** = major depressive episode; **MINI** = the Mini International Neuropsychiatric Interview; **SA** = suicidal attempt; **SI** = suicidal ideation; **PWE** = people with epilepsy.

Discussion

In patients with newly diagnosed focal epilepsy, the prevalence of mood, anxiety disorders, and suicidality is higher than in the general population and comparable to those of patients with established epilepsy. Their recognition at the time of the initial epilepsy evaluation is of the essence.

Suicidality encompasses passive and active suicidal ideation (SI), suicidal attempt (SA), and completed suicide. Their prevalence is higher in people with epilepsy (PWE) than in the general population[1,2] and patients with other neurologic disorders.[3] In a review of 12 studies, suicide accounted for 11.5% of deaths in PWE vs 1.6% in the general population.[4] Mood and anxiety disorders have been associated with suicidality in people with and without epilepsy.[4-8] In PWE, these psychiatric comorbidities may precede or follow the onset of epilepsy[9,10] or may be the expression of an iatrogenic effect from antiseizure medications (ASMs)[11,12] and/or epilepsy surgery.[13]

The prevalence of suicidality, mood, and anxiety disorders in patients with established epilepsy has been reported,[14,15] but there are little data on their prevalence in patients with newly diagnosed epilepsy and on the types of mood and anxiety disorders associated with suicidality. Although multiple studies have identified bipolar disorder (BPD) as a major risk for suicidality in the general population, this was demonstrated in only 2 studies of PWE.[4,16] Unfortunately, a population-based study that investigated completed suicide[6] in PWE grouped all mood disorders as a single variable. Furthermore, population-based studies[6,15] and retrospective health systems cohort studies[17-19] have identified an increased risk of completed suicide within the first 6 months after the onset of epilepsy.[6,15] Accordingly, early recognition of suicidality, mood, and anxiety disorders at the time of diagnosis of epilepsy is of the essence to prevent SAs.

The main aim of this study was to investigate the prevalence and clinical manifestations of suicidality and the specific types of mood and anxiety disorders associated with SI and SA in a cohort of adults with newly diagnosed focal epilepsy. A secondary aim was to assess whether ASMs with negative psychotropic properties are associated with these psychiatric comorbidities.

Methods

This study is part of the Human Epilepsy Project (HEP), a 6-year, prospective, observational, 29-site multicenter study setup to evaluate clinical, electrographic, and neuroimaging characteristics of patients with newly diagnosed focal epilepsy. Patients were 18–60 years old with documented focal epilepsy who had been started on an ASM within 4 months from the time of enrollment. The diagnosis was confirmed by the semiology core. Every patient underwent a high-resolution brain MRI and a 2-hour EEG study, which were also reviewed by the neuroimaging and EEG cores, respectively. Patients with a progressive epilepsy (e.g., brain tumors) were excluded. Patients enrolled in the study who on subsequent visits were found to have psychogenic-nonepileptic seizures or generalized epilepsy were excluded from the data analysis.

Standard Protocol Approvals, Registrations, and Patient Consents

Following local-site institutional review board approval, patients were enrolled after obtaining written informed consent. Enrollment took place from July 18, 2012, to September 28, 2017.

Evaluation of Psychiatric Phenomena

For this study, only mood and anxiety disorders and SI and SA were investigated.

Mood and Anxiety Disorders

At baseline, all patients underwent the Mini International Neuropsychiatric Interview (MINI), short version 5.0,[20] a structured interview designed to identify Axis I psychiatric diagnoses, according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV-TR).[21] The interview was administered by a trained research assistant, and the data were reviewed by a member of the comorbidity core.

For this study, we identified current and recurrent major depressive episodes (MDEs) with and without melancholia, current and past manic and hypomanic episodes, and dysthymia. Based on these diagnoses, 4 major diagnostic categories were established: (1) major depressive disorder (MDD), based on one or more MDEs with or without melancholia; (2) bipolar disorders type I (BPD-I), based on the presence of manic episode(s) with or without MDE(s), and BPD type II based on comorbid MDE(s) and hypomanic episode(s); (3) hypomanic episodes that occurred in the absence of an MDE were coded as hypomania; and (4) dysthymia. Patients with comorbid dysthymia and MDE or BPD were grouped with one of the latter 2 categories, as these are more severe types of mood disorders. A diagnosis of

BPD or hypomania was excluded in patients with episodes that met the criteria for manic and hypomanic episodes on the MINI who were treated with antidepressants since they can potentially trigger these episodes, a condition known as antidepressant-induced hypomania/mania.[22] We did not investigate the diagnosis of Interictal Dysphoric Disorder, an atypical manifestation of depression in PWE because it is not identified with the MINI, and it develops in patients with chronic epilepsy.[23,24]

Anxiety disorders included generalized anxiety disorder (GAD), panic disorder (current and lifetime) with and without agoraphobia, agoraphobia alone, and social phobia. Patients with a panic disorder who also had agoraphobia were grouped under the diagnosis of panic disorder.

Suicidality

The Columbia Suicidality Symptom Rating Scale (C-SSRS)[25] was used to investigate the clinical expressions of suicidality. It is a widely used instrument, which identifies the type of SI (active vs passive), its timing (lifetime vs current [in the last 6 months]), number of suicidal plans associated with active SI, and lifetime or current SAs (in the last 2 years). For this study, the expressions of suicidality were grouped into (1) any type of suicidality (e.g., lifetime, passive and/or active SI, and/or lifetime SAs), (2) lifetime active SI, (3) current active SI only, and (4) lifetime SAs. The number of lifetime suicidal plans was identified and compared between patients with and without SAs. The treating physician of patients with positive findings on the MINI and/or CSSRS was notified to ensure that they could make the appropriate referral to a mental health professional.

Association Between Antiseizure Medications and Mood, Anxiety Disorders, and/or Suicidality

We grouped ASMs according to their psychotropic properties into those with established negative (barbiturates, levetiracetam, topiramate, zonisamide, tiagabine, felbamate, and perampanel), positive (valproic acid, carbamazepine, oxcarbazepine, lamotrigine, gabapentin, pregabalin, and benzodiazepines), and not identified psychotropic properties (phenytoin, lacosamide, rufinamide, and cannabidiol).[26] We investigated the association between their psychotropic properties and any type of mood, anxiety disorders, and suicidality symptoms identified at the time of enrollment. Because patients could have been treated with ASMs for up to 4 months before enrollment, we identified those discontinued because of psychiatric adverse events.

Association Between the Duration of Epilepsy to Diagnosis and the Presence of Mood, Anxiety Disorders, and/or Suicidality

The duration of epilepsy, defined as the number of days between the onset of epilepsy and its diagnosis, was reported in a separate study.[27] We compared the duration of epilepsy between patients with and without psychopathology. In addition, we compared the percentage of patients with psychopathology between those whose epilepsy diagnosis was made within and after 6 months from its onset.

Statistical Analysis

Descriptive statistics and analyses were performed with IBM/SPSS v.26.0 software.[28] The Student t test was used to compare continuous variables between patients with and without a psychiatric diagnosis identified on the MINI and/or the C-SSRS. The χ^2 test with Yates continuity correction or Fisher exact test when appropriate and phi coefficient measurement were used to compare mood and anxiety disorder variable association between them and with the 4 expressions of suicidality (any type of SI, suicidal attempts, current active SI, and lifetime active SI). Furthermore, to identify the strongest explanatory variables of suicidality, we performed separate binomial logistic regression analyses with each of the dichotomous 4 expressions of suicidality as dependent variables and by forced entry of the same set of independent variables based on clinical interest. The list of explanatory variables included the type of mood and anxiety disorders that were identified to be significantly associated with at least 1 of the 4 expressions of suicidality in univariate analyses, and it also included age and sex as they had been identified as predictors of suicidality in studies conducted in PWE and the general population.[29,30] Correlations between variables were checked for possible collinearity, which was defined as r values ≥0.7 (and ≥0.3 for the phi coefficient), along with additional data screening, so statistical assumptions for logistic regression analysis could be checked. Significance was set at a p value <0.05. Correction for multiple comparisons was not considered to be necessary as the main findings were consistent when tested at different significant levels. We opted to provide a more detailed output of the statistical result, as we avoided additional approaches that could lead to reduce the power and miss results that might be subtle in this sample, but should be retested and performed differently in future studies.

Data Availability

Data not provided in the article because of space limitations may be shared (anonymized) by request to the lead author (A.M.K.) of any qualified investigator for purposes of replicating procedures and results.

Results

Among 366 patients who were initially enrolled, 19 were excluded because they were found to have psychogenic nonepileptic seizures and/or generalized epilepsy, leaving a total of 347 patients for analyses. No data were missing in these patients. eTable 1, links.lww.com/WNL/C550, summarizes their demographic, etiology, and suicidality data. Among these patients, 151 (43.5%) met the criteria for at least 1 mood and/or anxiety disorder and/or SI or SA: 134 (38.6%) had a mood and/or anxiety disorder, 58 (16.7%) of whom also endorsed suicidality symptoms, whereas in 17 patients (5%), only SI was identified. There was no difference in the age (36.7 ± 12.6 vs 37.1 ± 12.6), male sex (38.2% vs 42.8%), and the presence of structural pathology (13.4% vs 17.2%) between patients with and without psychopathology.

The prevalence rates of anxiety disorders were slightly higher (n = 95, 27.3%) than those of mood disorders (n = 82, 23.6%).

Comorbid mood and anxiety disorders were identified in 43 patients (12.4%). Among the 95 patients with an anxiety disorder, 62 experienced 1 type, 22 had 2, and 11 three types. Table 1 presents the prevalence of each type of mood and anxiety disorder identified on the MINI. Table 2 summarizes the prevalence of final diagnostic categories of mood and anxiety disorders, based on the criteria outlined in the method section and their prevalence among patients with any type of SI.

Table 1 Prevalence of Individual Types of Mood and Anxiety Diagnoses According to the MINI

Psychiatric Dx	N	% In the total cohort (N = 347)	% With psychiatric Dx (N = 151)
Mood disorders[a]			
Major depressive episodes without melancholia	24	6.9	15.9
Major depressive episodes with melancholia	23	6.6	15.2
Any major depressive episodes	47	13.5	31.1
Major depressive episodes, current	38	11	25.2
Major depressive episodes, recurrent	27	7.8	17.9
Major depressive episodes, past only	9	2.6	6
Dysthymia	11	3.2	7.3
Manic episodes, current only	3	0.9	2.0
Manic episodes, past only	7	2.0	4.6
Current + past manic episodes	2	0.6	1.3
Any manic episode	12	3.5	7.9
Hypomanic episodes, current only	4	1.2	2.6
Hypomanic episodes, past only	19	5.5	12.6
Hypomanic episodes, current + past	16	4.6	10.6
Any hypomanic episode	39	11.23	25.8
Manic + hypomanic episodes	4	1.2	2.6
Any mood disorder Dx	82	23.6	54.3
Anxiety disorders[a]			
Generalized anxiety disorder	50	14.4	33.1
Panic disorder	40	11.5	26.5
Agoraphobia	23	6.7	15.2
Social phobia	24	6.9	15.2
More than 1 anxiety disorder	33	9.5	21.8
Any anxiety disorder	95	27.4	62.9

[a] Prevalence higher than previously reported in the general population.[8,14]
MINI = Mini International Neuropsychiatric Interview.

Four major diagnostic categories of mood disorders were identified: MDD, BPD, hypomania, and only dysthymia. An MDD was identified in 33 patients (9.5%), 28 presenting with only MDEs, whereas 5 had a comorbid dysthymia. Only dysthymia was identified in 1 patient. BPD was identified in 24 patients (6.9%): BPD I in 12, based on MDEs and comorbid manic episodes in 5 patients, and in 7, based on only manic episodes. BPD II was seen in 12 patients, based on hypomanic and MDEs. Five patients with a BPD had a comorbid dysthymia. Only hypomania was identified in 23 patients (6.6%). Of note, 7 patients who had met the criteria for BPD (n = 3) or hypomania (n = 4) on the MINI were taking antidepressants. Accordingly, these diagnoses were removed. Bipolar spectrum disorder, which encompasses BPD and hypomania, was the biggest diagnostic group with 47 patients (13.5%). Among the major diagnostic categories of anxiety disorders, generalized anxiety disorder and panic disorder were the 2 most frequent, followed by agoraphobia and social phobia.

Comorbid Mood and Anxiety Disorders

Comorbid anxiety disorders were more frequent among patients with BPD (70.8%) than MDD (51.4%). Furthermore, there was a significant association between having more than 1 type of anxiety disorder and BPD (50%, $X^2 = 49.1$, df = 1, $p < 0.0001$, OR: 14.3 (95% CI: 5.7–35.9) but not with MDD (18%, $X^2 = 3.1$, df = 1, $p = 0.07$).

Suicidality

Seventy-five patients (21.6% of the total cohort and 50.3% of patients with a psychiatric diagnosis) experienced suicidality symptoms. A lifetime active SI and passive SI were identified in 48 (13.8%) and 27 (7.8%) patients, respectively. Among those with active SI, 18 endorsed 2 suicidal plans, 10 three, and 20 more than 3 plans.

Current SI, defined as SI in the last 6 months, was identified in 31 patients (8.9%): 16 had active SI and 15 passive SI. Among those with active SI, 11 endorsed 2 plans and 5 three or more.

Lifetime SAs were reported by 16 patients (4.6%), and in 4, the attempts occurred within the last 2 years. Among the 75 patients with any type of suicidality, the mean number of lifetime suicidal plans was significantly higher in those with (4.31 ± 1.4 [1–5]) than without attempts (1.95 ± 1.1 [0–5], $p < 0.0001$).

Association Between Mood, Anxiety Disorders, and Suicidality

Among patients with suicidality, 17 (22.7%) did not experience any anxiety or mood disorders, and none reported SAs; 12 endorsed only passive SI. Among the 58 patients with suicidality and mood and/or anxiety disorders, there was a higher frequency of comorbid mood and anxiety disorders (n = 29 [50%]) than of only anxiety (n = 20 [34.5%]) or only mood (n = 6 [10.3%]) disorders. Comorbid BPD and anxiety disorders (n = 15) were significantly more frequent than MDD and anxiety disorders (n = 9, $X^2 = 46.8$, df = 2, $p < 0.0001$), whereas the mean number of plans was higher among the former (3.42 ± 1.64) than the latter (2.75 ± 1.9, F = 7.33, $p = 0.001$).

Table 2 Final Diagnoses in the Entire Cohort, Patients With and Without Mood and Anxiety Disorders With and Without Suicidality

Final diagnosis	N	% Total, N = 347	% Patients with a psychiatric Dx, N = 151
Total major depressive disorder	33	9.5	21.8
Only major depressive disorder	28	**8.1**	**18.5**
Major depressive disorder + dysthymia	***5***	1.4	3.3
Total major depression + anxiety disorders	17	4.9	11.3
Only major depressive disorder + anxiety disorder	13	3.7	8.6
Major depressive disorder + dysthymia + anxiety disorder	4	1.2	3.3
Only dysthymia	1	0.2	0.6
Total bipolar disorder	24	6.9	15.9
Bipolar disorder type 1	12	3.45	7.9
Bipolar disorder type II	12	3.45	7.9
Bipolar disorder + dysthymia	5	1.4	3.3
Bipolar disorder + anxiety disorder(s)	17	4.9	11.3
Bipolar disorder + anxiety disorder + dysthymia	5	1.4	3.3
Only hypomania	23	6.6	15.2
Only hypomania + anxiety disorder(s)	7	2.0	4.6
Only anxiety disorders, total	52	15	34.4
Only mood disorders, total	39	11.2	25.8
Anxiety and mood disorders, total	43	12.4	28.5
Concurrent mood and anxiety disorders with and without suicidality			
Only anxiety disorders without suicidality	29	8.3	19.2
Only mood disorders without suicidality	31	8.9	20.5
Mood and anxiety disorders without suicidality	16	4.6	10.6
Total mood and anxiety disorders without suicidality	76	21.9	50.3
Suicidality without mood and anxiety disorders	17	4.9	11.3
Only mood disorders + suicidality	9	2.6	6
Only anxiety disorders + suicidality	20	5.8	13.2
Anxiety + mood disorders + suicidality	29	8.3	19.2
Total mood and anxiety disorders with suicidality	58	16.7	38.4
Total suicidality	75	21.6	50
Total number of patients with a psychiatric disorder	151	43.5	

Table 3 summarizes the univariate analyses and OR (OR) for the association between suicidality variables and the psychiatric disorders. The variables with significant association included the 4 types of anxiety disorders, having more than 1 type of anxiety disorder and having BPD and MDD (past and current) with and without dysthymia.

Table 4 summarizes the logistic regression analyses developed to identify the psychiatric explanatory variables of any form of suicidality, SAs, current active SI, and lifetime active SI. Independent variables included age, sex, generalized anxiety and panic disorders, social phobia, agoraphobia, BPD, and MDD with and without dysthymia. The models correctly classified from 84% to 96% of the cases in the 4 analyses. Bipolar disorders, MDD, and all anxiety disorders, except for social phobia, were significant explanatory variables for any type of suicidality, BPD, MDD, panic disorders, and agoraphobia for SAs, BPD, panic disorder, and agoraphobia for active lifetime SI and panic disorder for current active SI. Overall, BPD and panic disorders were the strongest explanatory variables for all 4 types of suicidality.

Effect of Antiseizure Medication on Mood, Anxiety Disorders, and Suicidality

Levetiracetam was the most frequently prescribed ASM (44.9%), followed by lamotrigine (24.2%), oxcarbazepine (7.3%), and carbamazepine (5.8%). Among all ASMs, 45% had positive and 49.8% negative properties. There was no difference in the type of ASM prescribed in patients with and without psychopathology.

Of note, 41 patients (11.2%) had been treated with an ASM that was discontinued before enrollment because of psychiatric adverse events: 37 (90.2%) were on levetiracetam. Twenty-one patients (51%) had a diagnosis of mood and/or anxiety disorder at the time of enrollment, but only in 7, the symptoms leading to ASM discontinuation were in the same diagnostic category as the diagnoses identified at the time of enrollment.

Association Between the Duration of Epilepsy and the Presence of a Psychiatric Diagnosis

There were no significant differences in the duration of epilepsy and the presence (median: 275 days) or absence (median: 219 days) of any mood and/or anxiety disorders and/or suicidality (p = 0.85, Mann-Whitney U). Furthermore, the prevalence rate of patients with any psychiatric diagnosis failed to differ between patients whose diagnosis was made before and after 6 months (p = 0.87). This finding was replicated when comparisons were made with each individual psychiatric diagnosis.

Psychiatric Treatment Before Enrollment

Among the 347 patients, 51 (14.7%) had been treated with a psychotropic medication before their enrollment in the study for mood, anxiety, and mixed mood and anxiety disorders. After enrollment, the MINI identified a mood and/or anxiety disorder in 35 of these patients (68.6%), 22 of whom (43.1%)

Table 3 Psychiatric Variables Associated With Suicidality

	Suicidality variables			
	Any type of SI	Suicidal attempts	Current active SI	Lifetime active SI
Psychiatric variables	OR (95% CI), *p* value	OR (95% CI), *p* value	OR (95% CI), *p* value	OR (95% CI), *p* value
Anxiety disorders				
GAD	6.09 (3.23–11.60, $p < 0.001$)	3.91 (1.28–11.09, $p = 0.012$)	5.21 (1.78–14.71, $p = 0.002$)	5.01 (2.49–9.96, $p < 0.001$)
Panic disorder	8.57 (4.27–17.75, $p < 0.001$)	5.24 (1.69–15.04, $p = 0.002$)	16.72 (5.81–52.24, $p < 0.001$)	13.21 (6.34–28.13, $p < 0.001$)
Agoraphobia	5.49 (2.31–13.43, $p < 0.001$)	7.90 (2.29–24.38, $p < 0.001$)	2.11 (0.32–8.23, $p = 0.344$)	5.79 (2.33–14.10, $p < 0.001$)
Social phobia	8.95 (3.76–22.99, $p < 0.001$)	5.18 (1.36–16.48, $p = 0.008$)	10.43 (3.25–31.53, $p < 0.001$)	6.54 (2.69–15.71, $p < 0.001$)
>1 anxiety disorder	11.59 (5.34–26.85, $p < 0.001$)	6.76 (2.16–19.68, $p = 0.001$)	16.45 (5.66–49.86, $p < 0.001$)	13.34 (6.11–29.91, $p < 0.001$)
Mood disorder				
Major depression	3.06 (1.43–6.41, $p = 0.003$)	4.92 (1.47–14.59, $p = 0.006$)	3.47 (0.92–10.71, $p = 0.041$)	2.19 (0.87–5.01, $p = 0.075$)
Bipolar disorder	11.10 (4.57–29.84, $p < 0.001$)	10.43 (3.25–31.53, $p < 0.001$)	7.46 (2.18–22.89, $p = 0.001$)	11.90 (4.95–29.65, $p < 0.001$)
Comorbid mood and anxiety disorders				
MDD + AD	3.57 (1.37–9.22, $p = 0.008$)	4.54 (0.97–15.92, $p = 0.028$)	4.54 (0.97–15.92, $p = 0.028$)	2.37 (0.74–6.54, $p = 0.115$)
BPD + AD	33.75 (9.20–217.81, $p < 0.001$)	17.45 (5.18–56.61, $p < 0.001$)	8.15 (2.07–27.33, $p = 0.001$)	19.60 (6.86–64.60, $p < 0.001$)

also endorsed SI (lifetime, n = 18; current, n = 4) on the CSSR-S. Seven of these 51 patients had met the criteria on the MINI for a manic (n = 2) or hypomanic episode (n = 5).

Discussion

Our study found a relatively high prevalence of mood, anxiety disorders, and suicidality in patients diagnosed with focal epilepsy within the previous 4 months. Their prevalence rates are higher than in general population studies and are comparable to those in patients with chronic epilepsy.[1,2,8,14,15] Our cohort's 21.6% prevalence of SI is similar to the 25% prevalence (95% CI 17.4%–32.5%) in national survey data in established PWE and twice as high (13.3% (95% CI 12.8–13.8) as in people without epilepsy,[8] whereas our prevalence of SAs (4.6%) is slightly lower than the pooled prevalence of 7.4% % (95% CI: 0.031–0.169) obtained in a meta-analysis from 18 studies of PWE.[17] Our cohort's prevalence of mood (23.6%) and anxiety disorders (27.3%) is comparable to the prevalence rates of depression [22.9% (95% CI: 18.2%–28.4%)] and anxiety [20.2% (95% CI: 15.3%–26.0%)] in meta-analyses of established PWE.[14] In studies that used a structured interview to identify anxiety disorders, a pooled prevalence of 27% (95% CI: 22.1%–33.3%)[14] was identical to that of our cohort. In addition to their high prevalence rates, the comorbid occurrence of mood and anxiety disorders in 1 of every 3 symptomatic patients and of SI in 1 of every 2 symptomatic patients illustrate the complexity of these psychiatric comorbidities at the time of diagnosis of focal epilepsy.

Bipolar disorders, MDD, panic disorder, and agoraphobia were explanatory variables of SI and SA, with BPD and panic disorders being the strongest variables. These findings are consistent with those reported in other studies and the general population.[29-33] The comparable prevalence of mood and anxiety disorders associated with suicidality in our study differs from the higher prevalence of mood than anxiety disorders identified in a population-based study from Denmark.[6] These differences could be accounted by the fact that the Danish study investigated the risk of completed suicide and our study of SI and SAs.

The comparable duration of epilepsy between patients with and without psychopathology was a counterintuitive finding. The onset of mood, anxiety disorders, and suicidality before that of epilepsy may provide one explanation for this observation. Indeed, several population-based studies have demonstrated a bidirectional relation between epilepsy and mood, anxiety disorders, and suicidality, whereby patients with these comorbidities have a two-to-four fold higher risk of developing epilepsy or seizures compared with people without psychiatric illness.[9,10,34] In our study, every patient had confirmed epilepsy through a rigorous adjudication process. Another explanation may reside on the fact that severe epilepsy that could influence the development of psychopathology had not yet occurred in many patients by the time of enrollment. This question is being investigated in a separate study.

Depression is typically reported as the most frequent psychiatric comorbidity in PWE. Yet, the comparable prevalence of anxiety and mood disorders in the studies cited above[8,14] and confirmed by our data highlights the need to place the same emphasis in identifying both comorbidities in PWE. Furthermore, the comparable prevalence rates of BPDs and

Table 4 Explanatory Factors of the 4 Types of Suicidality Outcomes (N = 347)

	Bivariate logistic regression					
					95% CI for odds ratio	
Independent variables	Wald	df	*p* Value	Odds Ratio	Lower	Upper
Any type of suicidal ideation[a]						
Age	0.39	1	0.531	0.99	0.97	1.02
Sex	0.34	1	0.557	1.21	0.64	2.31
Generalized anxiety disorder*	5.20	1	0.023	2.50	1.14	5.49
Panic disorder**	20.78	1	<0.001	6.78	2.98	15.43
Agoraphobia**	9.99	1	0.002	5.37	1.89	15.21
Social phobia**	1.72	1	0.190	2.18	0.68	6.95
Bipolar disorder**	10.09	1	0.001	6.13	2.00	18.76
Major depression and dysthymia*	6.26	1	0.012	3.18	1.29	7.89
Constant**	14.14	1	<0.001	0.12		
Suicidal attempts[a]						
Age*	4.22	1	0.043	1.05	1.00	1.11
Sex	0.00	1	0.989	0.99	0.29	3.45
Generalized anxiety disorder	0.10	1	0.758	0.81	0.21	3.08
Panic disorder**	7.73	1	0.005	8.02	1.85	34.83
Agoraphobia**	10.43	1	0.001	14.94	2.89	77.07
Social phobia	1.37	1	0.242	0.35	0.06	2.02
Bipolar disorder**	11.23	1	<0.001	17.85	3.31	96.29
Major depression and dysthymia**	10.39	1	0.001	12.03	2.65	54.62
Constant**	24.68	1	<0.001	0		
Current active suicidal ideation[a]						
Age	0.17	1	0.677	0.99	0.94	1.04
Sex	0.03	1	0.864	1.11	0.32	3.84
Generalized anxiety disorder	0.48	1	0.490	1.56	0.44	5.58
Panic disorder**	13.60	1	<0.001	11.03	3.08	39.52
Agoraphobia	0.15	1	0.697	1.53	0.18	13.20
Social phobia	1.63	1	0.202	2.62	0.62	11.50
Bipolar disorder	2.37	1	0.124	3.40	0.72	16.18
Major depression and dysthymia	2.88	1	0.090	3.92	0.81	18.99
Constant**	13.84	1	<0.001	0.02		
Lifetime active suicidal ideation[a]						
Age	0.38	1	0.537	1.01	0.98	1.04
Sex	0.04	1	0.846	0.92	0.42	2.04
Generalized anxiety disorder	1.05	1	0.306	1.62	0.65	4.04
Panic disorder**	35.47	1	<0.001	16.02	6.43	39.90
Agoraphobia**	13.87	1	<0.001	8.40	2.74	25.75

Continued

Table 4 Explanatory Factors of the 4 Types of Suicidality Outcomes (N = 347) *(continued)*

	Bivariate logistic regression					
					95% CI for odds ratio	
Independent variables	**Wald**	**df**	***p* Value**	**Odds Ratio**	**Lower**	**Upper**
Social phobia	0.14	1	0.706	0.79	0.22	2.77
Bipolar disorder**	12.41	1	<0.001	8.33	2.56	27.10
Major depression and dysthymia	3.32	1	0.068	2.82	0.93	8.62
Constant**	22.17	1	<0.001	0.03		

Notes: model = age, sex, generalized anxiety disorder, panic disorder, agoraphobia, social phobia, bipolar disorder, and major depression and dysthymia.
[a] Dependent variables analyzed.
Observation: all dependent and independent, categorical variables were coded 1 for the presence of the characteristic and 0 for the absence. Sex was coded 1 = female and 0 = male. Significance level: *$p \leq 0.05$; **$p \leq 0.01$.

MDDs in our study deserve special attention. Although the relatively high prevalence rate of BPD was an unexpected finding, it may be explained by the little attention paid to it in PWE. Yet, its early recognition is of the essence, given the important pathogenic role it plays on SI and SAs.

There are limited data on the role of BPD in suicidality in PWE, despite the recognition of manic and hypomanic symptoms in PWE since the beginning of the 20th century[35,36] In 1 multicenter observational study that included 139 PWE from 5 tertiary epilepsy centers, a lifetime history of manic episodes together with a history of MDEs carried the highest risk for suicidal attempts.[4] In a population-based study from Brazil that investigated the psychiatric variables associated with SI, BPD was found in 4.9% of PWE.[16] On the other hand, in the population study that investigated completed suicide in PWE in Denmark cited above,[6] the mood disorders were analyzed as a single variable, and hence, the individual role of BPD could not be ascertained. Another major population-based study from Iceland that demonstrated the role of suicidality on the risk of developing epilepsy also failed to investigate the prevalence rates of BPD associated with suicidality.[34]

Several studies have demonstrated a significant association between epilepsy and BPD. One population-based study that used the Oxford Record Linkage Study and the English National Linked Episode Statistics found that epilepsy and BPD occur together more frequently than expected by chance.[37] A Finnish population-based study found BPD to be significantly associated with epilepsy (OR: 2.53 [95% CI: 1.73–3.70]).[38] A recent meta-analysis based on 10 studies that included 48,334 PWE identified an overall pooled prevalence of BPD in PWE of 4.5% (95% CI: 2.2%–7.4%).[39] Of note, studies that used the MINI to make the diagnosis (n = 386) revealed a pooled prevalence of 9.4% (95% CI: 3.7%–17.1%). In addition, the pooled prevalence of bipolar symptoms was 12.3% (95% CI: 10.6%–14.1%) in that meta-analysis, which was identical to the findings of a population-based study that included a total of 85,358 patients aged 18 years or older that investigated the presence of symptoms of BPD among PWE, migraine, asthma, and diabetes.[40] Using the Mood Depression Questionnaire (MDQ), a validated screening instrument for symptoms of BPD types I and II.[41], bipolar symptoms were identified in 12% of PWE, which were 1.6–2.2 times more common than in patients with migraine, asthma, or diabetes and 6.6 times more likely to occur than in the healthy controls. Furthermore, 49.7% of PWE who endorsed bipolar symptoms (6%) were diagnosed with BPD, nearly twice the rate seen in other disorders. In our study, bipolar symptoms were identified in 47 patients (13.5%), in 24 (6.9%) as a BPD, and in 23 (6.6%) as only hypomania. These rates are almost identical to the 2 studies cited above.[38,39] These prevalence rates are significantly higher than those reported in the general population (1%–2% for BPD and 1.4% for hypomania).[42,43]

Failure to recognize primary BPDs is frequent in clinical practice, as patients with a mood disorder are 2 to 3 times more likely to report symptoms of depression than hypomania or mania.[42,43] In fact, up to 40% of patients with BPD are initially misdiagnosed with unipolar depression or other conditions with overlapping symptoms. Yet, distinguishing whether an MDE is part of an MDD vs BPD carries important clinical implications for the following reasons: (1) BPDs are more likely to be resistant to pharmacotherapy and require an early referral to a psychiatrist.[42,43] (2) BPD is associated with a high risk of SAs and completed suicide in the general population[31]; our data confirmed this observation. (3) Antidepressant drugs can trigger hypomanic and manic episodes in patients with BPD and can potentially worsen its course.[43] Suspicion that an MDE could be part of a BPD should be considered under the following circumstances: (1) a family history of BPD and (2) a first MDE in childhood or adolescence.

Whether the MINI can reliably identify BPD in PWE was questioned in a study that investigated the prevalence of BPD in 143 consecutive outpatients with chronic epilepsy, 85% of whom had persistent seizures.[44] Psychiatric symptoms were evaluated with the MINI, the MDQ, and the Interictal Dysphoric Disorder Inventory (IDDI), an instrument developed to identify this diagnosis.[45] Seventeen patients (11.9%) met the criteria for BPD with the MINI, and 21 (14.7%) had bipolar symptoms on the MDQ. Thus,

the prevalence of BPD by MINI was comparable to ours (8.5%), whereas their MDQ data were identical to that of Ettinger's study.[40] Yet, because a diagnosis of IDD was made in 6 patients and in 9, bipolar symptoms were interpreted as being either peri-ictal or iatrogenic symptoms caused by ASMs, the authors concluded that only 2 patients (1.4%) had met the criteria for a pure BPD diagnosis. Although these observations must be considered in the analysis of bipolar symptoms in PWE, they likely do not apply to our patients for the following reasons: (1) IDD and peri-ictal symptoms occur in patients with established treatment-resistant epilepsy of at least 2 years of duration,[44,45] whereas our patients were newly diagnosed. (2) In our study, the occurrence of psychiatric symptomatology did not differ as a function of exposure to ASMs with negative psychotropic properties.

Mood and anxiety disorders and suicidality may be caused by ASMs.[26] Yet, in our study, the same proportion of symptomatic and asymptomatic patients were taking an ASM with negative (49% vs 50.3%) and positive (46.3% vs 43.8%) psychotropic properties at the time of enrollment. The short duration of pharmacotherapy by the time of enrollment may explain our failure to prove a psychiatric iatrogenic effect of ASMs with negative psychotropic properties. In fact, among 41 patients who discontinued their ASM because of psychiatric adverse events before enrollment, 90% were taking levetiracetam. Nonetheless, the effect of ASMs on psychiatric comorbidities in our cohort will have to wait for the results of an ongoing study that is investigating the causes for discontinuation of ASMs over a 4-year follow-up period.

We recognize the multifactorial pathogenic mechanisms operant in the suicidality risks of PWE, but we decided to focus this study to the investigation of the role of mood and anxiety disorders only as they are the most frequent psychiatric comorbidities in these patients. Accordingly, the lack of inclusion of other psychiatric disorders or economic and social data is an important limiting factor of our study. Indeed, other psychiatric comorbidities (e.g., substance, alcohol abuse, and personality disorders) and socioeconomic variables may have played a pathogenic role in the suicidality risks of these patients.[45,46] In fact, 17 patients with SI who failed to meet the criteria for any mood and/or anxiety disorders in our study illustrate the potential pathogenic role of other psychiatric disorders in the development of SI and should be investigated even if their prevalence is lower in PWE.

In addition, the patients included in this study had been enrolled in tertiary epilepsy centers that typically evaluate patients with more severe forms of epilepsy. Accordingly, they may not be representative of all patients with newly diagnosed focal epilepsy.

Finally, not all types of mood and anxiety disorders are explanatory factors in all forms of suicidality. The reason for this phenomenon cannot be explained at this point.

Mood and anxiety disorders and suicidality are interrelated complex psychiatric comorbidities, which are identified with a relatively high frequency at the time of the diagnosis of epilepsy. Our data demonstrated that their prevalence rates are comparable to those reported in population-based studies in patients with an established epilepsy and highlight the pivotal role of MDD, BPD, panic disorders, and agoraphobia as risk factors of SI and SAs. Our findings reveal that PWE and the general population have the same risk factors for suicidality and given their presence at the time of diagnosis of epilepsy, need to be investigated as part of the initial comprehensive evaluation of the seizure disorder. Given that completed suicide has been found to occur in the first 6 months after diagnosis in population-based studies,[6] the early recognition of risk factors of SAs can minimize their occurrence. A brief review of the screening of comorbid mood and anxiety disorders in an outpatient neurology clinic is provided in eAppendix 1, links.lww.com/WNL/C549. In summary, an evaluation of patients with newly diagnosed focal epilepsy must be considered incomplete if it failed to include an investigation of comorbid mood, anxiety disorders, and suicidality.

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Continued

Appendix *(continued)*

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Appendix *(continued)*

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