FULL-LENGTH ORIGINAL RESEARCH

Concurrent mood and anxiety disorders are associated with pharmacoresistant seizures in patients with MTLE

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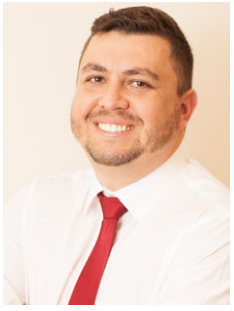
Epilepsia, **(*):1–9, 2017
doi: 10.1111/epi.13781



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Summary

Objective: To investigate whether mood disorders (MD) and anxiety disorders (AD) are associated with seizure control in patients with mesial temporal lobe epilepsy (MTLE). We compared patients without any current psychiatric disorder, patients with current MD and/or AD, patients with subsyndromic depression episodes (SSDE) and anxiety episodes (SSAE), and patients with family psychiatric history.

Methods: In a cross-sectional study, we included 144 consecutive patients with MTLE (82 pharmacoresistant and 62 treatment-responsive patients). Every patient underwent a psychiatric evaluation including the Structured Clinical Interview for DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition) Axis I (SCID-I), Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI), Neurological Disorders Depression Inventory for Epilepsy (NDDI-E), and Interictal Dysphoric Disorder Inventory (IDDI). Patients were divided into four groups: PsychNeg (G1, n = 61), current SSDE and SSAE (G2, n = 26), Current MD or AD (G3, n = 25), and current mixed MD/AD (G4, n = 32).

Results: Among patients with pharmacoresistant MTLE, 68.3% (56/82) experienced symptoms of depression and/or anxiety (G2, G3, and G4) (odds ratio [OR] 2.8, 95% confidence interval [CI] 1.41–5.53, $p < 0.01$). Patients with mixed MD/AD (G4, n = 24/32) were more likely to have pharmacoresistant MTLE (OR 4.04, 95% CI 1.57–10.42, $p < 0.01$) than psychiatric asymptomatic patients (G1, n = 26/61), and their seizure frequency was significantly higher ($p < 0.01$). Positive family psychiatric history was more frequent in pharmacoresistant patients (n = 27/82, OR 2.28, 95% CI 1.02–5.05, $p = 0.04$). Finally, 31.6% of patients with MD and or AD were not receiving psychiatric treatment.

Significance: Identification of comorbid MD/AD and of family psychiatric history is of the essence in patients with MTLE, as they appear to be associated with worse seizure control.

KEY WORDS: Epilepsy, Depression, Anxiety, Subsyndromic depression, Family psychiatric history.

The relationship between epilepsy and psychiatric disorders is complex and largely remains poorly understood. However, the presence of psychiatric disorders in patients with epilepsy (PWE) may reflect a dysfunction that preceded the onset of seizure disorder and/or a multifactorial interplay between psychosocial, iatrogenic, neurophysiologic, and neurochemical changes associated with seizure disorder and the neurologic insult that resulted in epilepsy.[1,2] In particular, a high prevalence of psychiatric

Accepted April 7, 2017.

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Key Points

- Psychiatric disorders (MD and/or AD) occurred in 39.6% of MTLE patients and subsyndromic forms of depression and anxiety in 18%
- Pharmacoresistant epilepsy was significantly associated with current mixed mood and anxiety disorders
- Positive family psychiatric history was associated with pharmacoresistant MTLE

disorders has been long recognized among patients with mesial temporal lobe epilepsy (MTLE), given the common pathogenic role played by limbic structures in both conditions.[1,3]

Mood disorders (MD), followed by anxiety disorders (AD), are the most frequent psychiatric disorders in epilepsy, with a lifetime history of approximately 30–35%.[1,3–5] Yet these comorbid psychiatric disorders remain underdiagnosed and untreated and can present either as primary MD and AD, described in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)[6] based on predetermined diagnostic criteria, or as subsyndromic depressive (SSDE) and anxiety (SSAE) episodes.[7,8] Although psychiatric comorbidities have been found to be more frequent among patients with pharmacoresistant epilepsy, there are no data on whether the type and severity of psychiatric comorbidity differ on their association with seizure control.

Family psychiatric history is an important risk factor for psychiatric disorders in patients with and without epilepsy,[9] as genetic factors play pivotal pathogenic mechanisms in most psychiatric disorders.[10] However, the role of psychiatric family history on seizure control has never been investigated.

The aims of this study were to investigate whether antiepileptic drug (AED) treatment response differs (1) among patients with MTLE with Axis I DSM-IV defined MD and/or AD, versus SSDE and/or SSAE versus asymptomatic patients; (2) the severity of symptoms of depression and anxiety; and (3) with the existence of a family psychiatric history.

Methods

Patient selection

We conducted a cross-sectional study including prospective data from structured psychological instruments in 165 consecutive patients with MTLE diagnosed according to International League Against Epilepsy (ILAE) criteria (https://www.epilepsydiagnosis.org/seizure/temporal-overview.html)[11,12] with and without hippocampal sclerosis and no surgical treatment prior to the enrollment. There were 104 women and 61 men, with mean age (±standard deviation [SD]) of 46.09 (±11.30 years). Patients were enrolled consecutively from March 2010 to June 2014 at the outpatient Epilepsy Clinics of University of Campinas (UNICAMP, São Paulo, Brazil), a tertiary epilepsy center (Details in Data S1).

Clinical and sociodemographic variables

Clinical data were collected from patients' medical records, including seizure type and monthly frequency from the previous 2 years, age at onset, duration, family history of epilepsy (only relatives of first and second degree), magnetic resonance imaging (MRI) data (side of hippocampal atrophy) (see MRI acquisition protocols in Data S1), and current AEDs. Sociodemographic data included age, gender, marital status, and educational level.

Patients were considered to present pharmacoresistant MTLE (82 subjects) if focal seizures with loss of consciousness and/or secondarily generalized tonic–clonic seizures had failed to remit to at least two optimal AEDs trials taken as monotherapy or polytherapy, according to the recent ILAE definition of pharmacoresistant epilepsy.[13] Patients were considered to be AED treatment-responsive (62 subjects) if they remained free from disabling seizures (focal motor without loss of consciousness, focal seizures with loss of consciousness and secondarily generalized tonic–clonic seizures) for at least 1 year. Patients with rare auras (which occurred in only four patients) were considered treatment-responsive. The University Ethics Committee approved the study protocol, and all assessed patients signed the consent form prior to their inclusion in the study.

Psychiatric assessment

Patients underwent a structured interview with the Structured Clinical Interview for DSM-IV (SCID-I), which generates current and past Axis I categorical diagnoses.[14] The psychiatric assessment was administered by a psychologist with extensive experience in epilepsy and psychiatric disorders. After diagnosis of MD or AD, the epileptologists were informed and patients were referred for psychiatric follow-up when necessary. For this study, only Axis I current diagnoses (MD, and/or AD) were considered. Additional data on past psychiatric disorders and psychiatric family history (first- to third-degree relatives) were collected from a structured neuropsychiatric interview with additional open questions.

To assess the presence of symptoms of depression and anxiety in patients whose SCID-I failed to identify an Axis I diagnosis of MD and/or AD, and quantify the severity of symptoms in those that did, patients completed four self-rating screening instruments (using the validated Brazilian version): (1) Beck Depression Inventory (BDI),[15] (2) Beck Anxiety Inventory (BAI),[16] (3) Neurological Disorders Depression Inventory for Epilepsy (NDDI-E, developed to screen specifically current Major Depressive Episode [MDE] with scores >15),[17] and (4) Interictal Dysphoric Disorder Inventory (IDDI – developed to identify the

Interictal Dysphoric Disorder [IDD], an atypical but frequent presentation of depression in patients with epilepsy)[18] (Table 2). (Details are presented in Data S1.) Therefore, only current psychiatric symptoms were considered a positive sign of SSDE, SSAE, MD, and/or AD.

The 165 MTLE patients were classified according the following criteria:

1 *Psychiatric negative*: (PsychNeg) 77 subjects without any psychiatric categorical Axis I on the SCID and with BDI score <12, BAI <10, NDDI-E <15. Of the group of 77 patients, we excluded 16 patients who had a past psychiatric history of mood disorder and were under psychotherapy treatment and/or had taken antidepressants. Because we were not able to assume that these previous diagnoses were reliable, we decided to not include these patients in our study; however, their data are available in the Data S1 and Table S1. Therefore, the PsychNeg group was composed of 61 patients;
2 *Current SSDE and/or SSAE*: included 26 subjects with BDI score >11 and/or BAI score >9, in the absence of any DSM-IV Axis I diagnosis;
3 *Current MD or AD*: included 25 subjects with MD or AD (but not both simultaneously) according to DSM-IV Axis I diagnosis;
4 *Current mixed MD/AD:* included 32 subjects with concurrent MD and AD (n = 11, according to DSM-IV criteria), or with one of the associations: current MD + SSAE or AD + SSDE (n = 21).
5 *Current IDD:* included five subjects who met criteria on the IDDI, in the absence of any DSM-IV Axis I diagnoses. To perform analyses with more homogeneous and balanced groups we excluded this group due to the small number of subjects.

The final sample included 144 MTLE patients (89 women) with a mean age of 45.64 ± 10.34 years (82 pharmacoresistant and 62 treatment-responsive).

Data analysis

Statistical analyses were performed using SPSS21 (Armonk, NY, U.S.A.) with level of significance set at $p < 0.05$. Chi-square statistics were used to compare proportions and Mann-Whitney or Kruskal-Wallis for continuous variables, when necessary. Multiple comparisons were corrected with Bonferroni adjustments. The analyses included the following:

1 Comparison of family psychiatric history between treatment-responsive patients and those with pharmacoresistant MTLE.
2. Comparison of seizure frequency among the four groups.
3. Comparison of BDI and BAI scores between treatment-responsive patients and those with pharmacoresistant MTLE.
4. Correlation between seizure frequency and BDI and BAI scores. For this analysis, we used Spearman correlation.
5. Comparison of seizure control and positive screening for MDE, established with a total score >15 on NDDI-E.
6. Comparison of gender, age, educational level, age at onset, and duration of epilepsy between treatment-responsive patients and those with pharmacoresistant MTLE.

Results

The clinical and sociodemographic data from 144 MTLE patients included in our analysis are displayed in Table 1. The psychiatric diagnoses groups were balanced with respect to age (Kruskal-Wallis test, $p = 0.91$), epilepsy onset (Kruskal-Wallis test, $p = 0.97$), and epilepsy duration (Kruskal-Wallis test, $p = 0.71$), but not so with respect to gender (chi- square test, $p = 0.01$), because the group with current MD or AD (G3) had more women (n = 21/25, chi-square test, $p < 0.01$) than the PsychNeg group (G1, n = 27/61) did.

Prevalence of MD, AD, SSDE, and SSAE symptoms in MTLE patients

Among the 144 patients, 83 (57.6%) were experiencing current psychiatric symptoms (G2, G3, and G4) of depression and/or anxiety. Psychiatric diagnoses and scores on BDI and BAI are presented in Table 2. Major depressive disorder (MDD) was the most frequent MD identified (n = 44; 30.5%), whereas among AD, simple phobia (n = 11; 7.6%), panic disorder (n = 4; 2.8%), and generalized anxiety disorder (n = 5; 3.5%) were identified. Thirty-two patients (22.2%) had mixed MD/AD. Current SSDE and/or SSAE symptoms were observed in 26 patients (18%) but we did not observe any statistical differences in this group when compared to the other groups.

Relationship between pharmacoresistance and psychiatric symptoms

Of the 144 patients, 82 (57%) had pharmacoresistant MTLE. Table 3 shows the clinical and sociodemographic characteristics, as well as scores on BDI, BAI, and NDDI-E for pharmacoresistant and treatment-responsive patients. The two groups were balanced for age (Kruskal-Wallis test, $p = 0.72$), epilepsy onset (Kruskal-Wallis test, $p = 0.51$), epilepsy duration (Kruskal-Wallis test, $p = 0.11$), and gender (chi-square test, $p = 0.91$). Among 82 patients with pharmacoresistant MTLE, 56 (68.3%) exhibited current psychiatric symptoms, whereas 27 patients (43.5%) presented psychiatric symptoms in the treatment-responsive group. The odds ratio for pharmacoresistance in patients with current psychiatric symptoms was 2.8 (95% CI 1.41–5.53, $p < 0.01$). The group with current mixed MD/AD (G4) also had more patients

Table 1. Clinical and sociodemographic characteristics of MTLE patients included in our analysis

Groups	PsychNeg (G1) N = 61 mean (SD), or median (range), or N (%)	SSDE and SSAE (G2) N = 26 mean (SD), or median (range), or N (%)	MD or AD (G3) N = 25 mean (SD), or median (range), or N (%)	Mixed MD/AD (G4) N = 32 mean (SD), or median (range), or N (%)	p-Value
Age (years)	45.1 (±11.2)	46.5 (±10.8)	46 (±8.3)	44.9 (±11.2)	0.91
Duration of epilepsy	32.5 (±12.9)	33.1 (±12.7)	33.3 (±13.9)	30 (±14.2)	0.71
Age at epilepsy onset	10 (1–35)	8 (0–40)	11 (1–41)	10.5 (0–48)	0.97
Monthly frequency of seizures	0 (0–12)	1 (0–8)	1 (0–12)	3 (0–20)	<0.01
Educational level (years)	6 (0–15)	4.5 (0–16)	4 (2–18)	6.5 (1–13)	0.78
Gender					<0.01
Female	27 (44.3)	19 (73)	21 (84)	22 (69)	
Marital status					0.53
Single	25 (41)	7 (27)	11 (44)	14 (44)	
Married	36 (59)	19 (73)	14 (56)	18 (56)	
Family history of epilepsy					0.12
Yes	19 (31)	12 (46.2)	13 (52)	17 (53.1)	
No	42 (69)	14 (54)	12 (48)	15 (47)	
Family history of psychiatric disorders					<0.01
Yes	8 (13)	3 (11.5)	9 (36)	18 (53)	
No	53 (87)	23 (88.5)	16 (64)	14 (47)	
Seizure type					0.04
Treatment-responsive	31 (51)	10 (38.5)	9 (36)	8 (25)	
Auras	4 (6.6)	–	–	–	
Dyscognitive seizures with or without auras	9 (14.8)	3 (11.5)	7 (28)	11 (34.4)	
Dyscognitive seizures with secondarily generalized tonic–clonic seizures	17 (28)	13 (50)	9 (36)	13 (40.6)	
Pharmacoresistance					0.01
Yes	26 (43)	16 (61.5)	16 (64)	24 (75)	
No	35 (57)	10 (38.5)	9 (36)	8 (25)	
MRI (side of hippocampal atrophy)					<0.01
MRI-negative	19 (31.2)	3 (11.5)	10 (40)	5 (15.6)	
Left	16 (26)	19 (73.1)	5 (20)	12 (37.5)	
Right	18 (29.5)	1 (3.8)	8 (32)	10 (31.3)	
Bilateral	6 (10)	2 (7.7)	2 (8)	3 (9.4)	
Undefined	2 (3.3)	1 (3.8)	–	2 (6.3)	
Antiepileptic drugs					<0.01
Monotherapy	24 (39.3)	2 (8)	5 (20)	6 (19)	
Polytherapy	36 (59)	23 (88)	20 (80)	26 (81)	
No drugs	1 (1.6)	1 (4)	–	–	

PsychNeg, negative psychiatric symptoms; SSDE, subsyndromic forms of depressive episodes; SSAE, subsyndromic forms of anxiety episodes; MD, mood disorders; AD, anxiety disorders; SD, standard deviation; MRI, magnetic resonance imaging.

with pharmacoresistant epilepsy (n = 24/32) than the asymptomatic (G1, n = 26/61, chi-square test, p = 0.02), as shown in Figure 1A. Pharmacoresistance was 4.04 times more likely to occur in the group with current mixed MD/AD (95% CI 1.57–10.42, p < 0.01) than in those PsychNeg. As expected, seizure frequency was higher for patients with current mixed MD/AD (G4) when compared with PsychNeg, (G1) (Kruskal-Wallis test, p < 0.01) (see also Table 1 and Fig. 1B). On the other hand, seizure control was similar among patients with only MD or AD (Kruskal-Wallis test, p = 0.84).

Relation between family psychiatric history and seizure control

Family psychiatric history was identified in 38 patients (31 first-degree, 4 second-degree, and 3 third-degree relatives) and was associated with pharmacoresistant MTLE (n = 27/82, chi-square test, p = 0.04) with an odds ratio of 2.28 (95% CI 1.02–5.05), as shown in Table 3.

Relationship between seizure control and psychiatric scores on the BDI and BAI and NDDI-E

A multivariate analysis revealed differences of total BDI and BAI scores between pharmacoresistant and treatment-responsive groups (multivariate analysis of variance [MANOVA], Pillai's Trace = 0.06, $F_{2,141} = 4.8$, p < 0.01, partial $\eta^2 = 0.06$). When applying Bonferroni adjustment with an alpha level set to 0.025 to control for multiple comparisons, pharmacoresistant patients had significantly higher scores on BDI (mean difference 5.13, p < 0.01, 95% CI 1.7–8.6) and BAI (mean difference 2.72, p < 0.01, 95% CI 0.76–4.68) (Table 3, Fig. 2).

Table 2. Type, frequency and associations among MD, AD (according to DSM-IV criteria), and SSDE/SSAE

Groups	Psychiatric disorder	N (%)	BDI scores median (range)	BAI scores median (range)	NDDI-E N (%) positive depression (scores >15)
PsychNeg (G1)	Any current psychiatric disorder	61 (42.4)	2 (0–7)	0 (0–8)	0 (0)
SSDE and SSAE (G2)		26 (18.1)	12 (1–16)	5.5 (0–13)	6 (4.2)
	Subsyndromic depressive episode	17 (11.8)			
	Subsyndromic anxiety episode	7 (4.9)			
	Subsyndromic depressive/anxiety episode	2 (1.4)			
MD or AD (G3)		25 (17.4)	14 (3–24)	4 (0–18)	13 (9)
	Major depressive episode	1 (0.7)			
	Major depressive disorder	14 (9.7)			
	Dysthymic disorder	4 (2.8)			
	Specific phobia	2 (1.4)			
	Generalized anxiety disorder	1 (0.7)			
	Generalized anxiety disorder + specific phobia	1 (0.7)			
	Panic disorder + specific phobia	2 (1.4)			
Mixed MD/AD (G4)		32 (22.2)	27 (13–41)	12 (2–30)	28 (19.4)
	Major depressive disorder + subsyndromic anxiety episode	19 (13.2)			
	Bipolar disorder type II + subsyndromic anxiety episode	1 (0.7)			
	Specific phobia + subsyndromic depressive episode	1 (0.7)			
	Major depressive disorder + generalized anxiety disorder	3 (2.1)			
	Major depressive disorder + panic disorder	2 (1.4)			
	Major depressive disorder + specific phobia	4 (2.8)			
	Major depressive disorder + obsessive compulsive disorder	1 (0.7)			
	Bipolar disorder type II + specific phobia	1 (0.7)			
	Total=	144			
General psychiatric diagnosis	Current psychiatric symptoms	83 (57.6)			
	Current mood disorders	50 (34.7)			
	Past mood disorders	45 (31.2)			
	Current anxiety disorders	18 (12.5)			
	Past anxiety disorders	8 (5.5)			

PsychNeg, negative psychiatric symptoms; SSDE, subsyndromic forms of depressive episodes; SSAE, subsyndromic forms of anxiety episodes; MD, mood disorders; AD, anxiety disorders; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; BDI, Beck Depression Inventory; BAI, Beck Anxiety Inventory; NDDI-E, Neurological Disorders Depression Inventory for Epilepsy.

The frequency of patients with positive screen of MDE according to NDDI-E (scores >15) was significantly higher in the pharmacoresistant group (n = 37/82) compared to the treatment-responsive group (n = 10/62, chi-square test, $p < 0.01$; Table 3).

We detected a weak correlation between seizure frequency and both BDI (Spearman correlation, $r = 0.28$, $n = 144$, $p < 0.01$) and BAI scores (Spearman correlation, $r = 0.26$, $n = 144$, $p < 0.01$).

Psychiatric pharmacologic and nonpharmacologic treatment

As illustrated in Figure 3, 18 patients (31.6%) with diagnosis for depression and/or anxiety were not receiving treatment for these comorbidities (G3, n = 8/25; G4, n = 10/32), and neither were 69% of the subjects with subsyndromic episodes of depression and anxiety. At the time of this study, all symptomatic patients without psychological and/or psychiatric treatment were referred to mental health professionals.

Discussion

The main findings of this study are the association between pharmacoresistance in MTLE patients and (1) co-occurrence of mood and anxiety disorders and (2) family psychiatric history.

Similar to previous reports, we found that 57 patients (39.6%) met diagnostic criteria for MD (34.7%), AD (11.8%), or both (22.2%).[4] In addition, we demonstrated that patients with psychiatric diagnosis were more likely (OR 2.8) to present refractory seizures, which is also in accordance with previous studies.[9,19,20] One study[19] evaluated 780 patients newly diagnosed with epilepsy and found that psychiatric comorbidity preceding the onset of the epilepsy was associated with pharmacoresistance with an OR of 2.17. In another study with 138 patients with newly diagnosed epilepsy,[21] the presence of symptoms of depression and anxiety before institution of pharmacotherapy reduced the likelihood of complete seizure remission after 12 months of treatment. Despite this evidence, our study is

Table 3. Clinical, sociodemographic characteristics, and scores on BDI, BAI, and NDDI-E of pharmacoresistant and treatment-responsive patients

Patients	Pharmacoresistant group N = 82 mean (SD), or median (range), or N (%)	Treatment-responsive group N = 62 mean (SD), or median (range) or N (%)	p-Value
Age (years)	45.3 (±9.3)	45.6 (±12.2)	0.71
Duration of epilepsy	33.6 (±12.4)	30.2 (±14.1)	0.1
Age of epilepsy onset	8 (0–42)	12 (1–48)	0.051
Monthly frequency of seizures	3 (0.3–20)	0	<0.01
Educational level (years)	5 (0–16)	5.5 (0–18)	0.62
Gender			0.91
Female	51 (62.2)	38 (61.3)	
Marital status			0.61
Single	31 (37.8)	26 (42)	
Married	51 (62.2)	36 (58)	
Family history of epilepsy			0.92
Yes	35 (42.7)	26 (42)	
No	47 (57.3)	36 (58)	
Family history of psychiatric disorders			0.04
Yes	27 (33)	11 (17.7)	
No	55 (67.1)	51 (82.3)	
MRI (side of hippocampal atrophy)			0.43
MRI-negative	18 (22)	19 (30.6)	
Left	31 (37.8)	21 (33.9)	
Right	24 (29.3)	13 (21)	
Bilateral	6 (7.3)	7 (11.3)	
Undefined	3 (3.7)	2 (3.2)	
Antiepileptic drugs			0.03
Monotherapy	16 (19.5)	21 (33.9)	
Polytherapy	66 (80.5)	39 (63)	
No drugs	–	2 (3.2)	
BDI scores	12 (0–41)	4 (0–37)	<0.01
BAI scores	5 (0–30)	2 (0–26)	<0.01
NDDI-E positive depression (>15)	37 (45.1)	10 (16.1)	<0.01

SD, standard deviation; MRI, magnetic resonance imaging, BDI, Beck Depression Inventory; BAI, Beck Anxiety Inventory; NDDI-E, Neurological Disorders Depression Inventory for Epilepsy.

the first to demonstrate an association between *joint* occurrence of mood and anxiety disorders (and their subsyndromic forms) and a worse seizure control with AEDs (OR 4.04). However, the impact of such combination had been associated previously with poorer quality of life (QoL) compared to the isolated occurrence of AD or MD,[22] including subjects with AD combined with subsyndromic forms of depression.[7] Our findings support prior studies showing that the poorer QoL is related to refractory seizures.[22]

Although psychiatric comorbidity has been associated with refractory seizures,[9] the association between a family psychiatric history and a higher risk of treatment-resistance in MTLE was not reported previously, which in our study was the second important factor related to pharmacoresistance. The recognition of a family psychiatric history can help the identification of patients with a risk to develop psychiatric disorders and possibly avoid serious complications such as suicide.[9] A family psychiatric history is also correlated to an increased risk of iatrogenic psychiatric adverse events with the introduction of several AEDs.[23] Moreover, patients with a family psychiatric history are more likely to present pathologic reactions to stressful situations.[9] Although undervalued, family psychiatric history plays an important role in pharmacoresistance[9,23] and therefore deserves further investigation.

The relationship between psychiatric disorders and epilepsy is complex and raises the question of whether psychiatric disorders are comorbidities merely associated with treatment-resistant seizure or are directly involved in induction/facilitation of treatment-resistance.[24] The intuitive hypothesis is that pharmacoresistant seizures cause depression and anxiety symptoms in PWE. However, population-based studies have suggested a bidirectional relationship between epilepsy and psychiatric disorders.[25] For example, a longitudinal study[25] evaluated the temporal associations between psychiatric disorders and epilepsy in a cohort of 3,773 PWE and 14,025 controls, and demonstrated that not only did PWE have a higher risk of developing psychiatric disorders, but that patients with primary psychiatric disorders also had a higher risk for developing epilepsy, which is in agreement with other studies.[20,26] These findings do not imply that psychiatric disorders cause epilepsy or vice

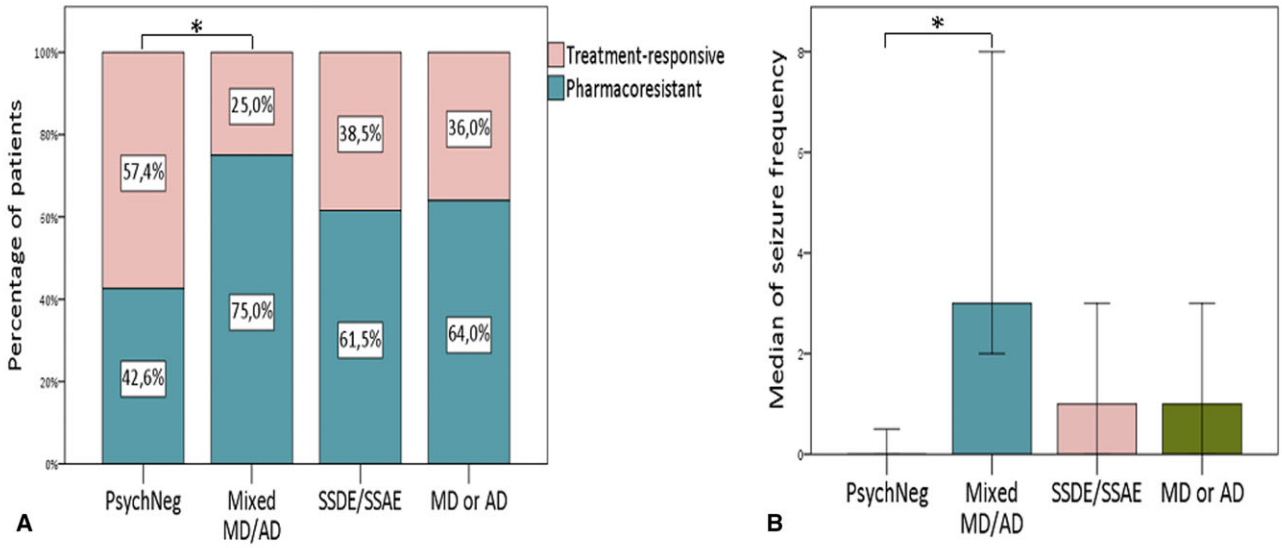

Figure 1.
(**A**) Distribution of pharmacoresistant and treatment-responsive patients according to the psychiatric diagnosis; group with mixed MD/AD presented more pharmacoresistant patients than the PsychNeg group (*) $p = 0.02$. (**B**) Seizure frequency (monthly) according to psychiatric groups; group with mixed MD/AD presented higher seizure frequency than PsychNeg group (*) $p < 0.01$. PsychNeg, asymptomatic psychiatric symptoms; MD, mood disorders; AD, anxiety disorders; SSDE, subsyndromic forms of depressive episodes; SSAE, subsyndromic forms of anxiety episodes.

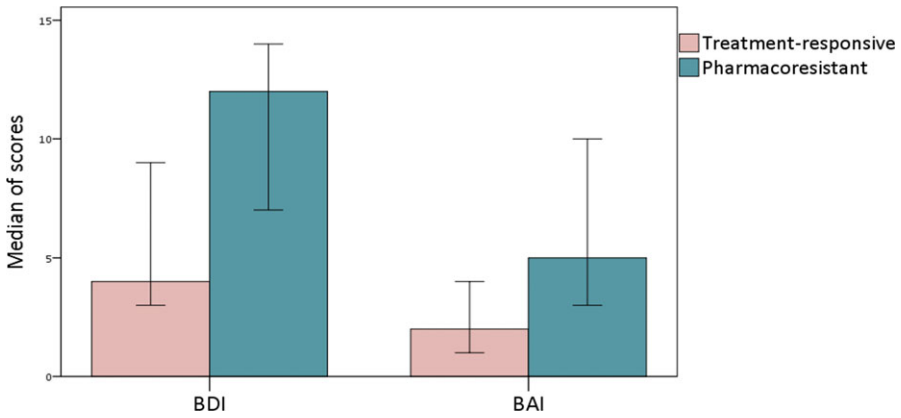

Figure 2.
Median of scores on BDI and BAI according to pharmacoresistance. BDI ($p < 0.01$) and BAI ($p < 0.01$) were significantly higher in pharmacoresistant patients. BDI, Beck Depression Inventory; BAI, Beck Anxiety Inventory.

versa, but strongly suggest the existence of common pathogenic mechanisms associated with both epilepsy and psychiatric disorders.

In fact, several pathogenic mechanisms of mood and anxiety disorders have been found to facilitate the development of seizures in animal models of epilepsy.[24,27–30] These include endocrine disturbances such as high serum concentrations of cortisol as a result of a hyperactive hypothalamic–pituitary–adrenal axis,[27] inflammatory mechanisms including the effects of the interleukin (IL)-1β in the rat hippocampus,[28] and disorders of neurotransmitters such as dopamine, serotonin,[31] norepinephrine,[32] glutamate,[29] and γ-aminobutyric acid (GABA).[30] Besides the endocrine, inflammatory, and neurotransmitter disturbances, one additional hypothesis for the association between combined MD and AD and increased risk of pharmacoresistance, is that compared to isolated MD or AD, patients with combined symptoms are more likely to present higher levels of stress, insomnia, and worse sleep quality, which are factors related to increased seizure frequency.[33–35] One study[36] evaluated the impact of stress on the seizure occurrence and found that sleep deprivation, higher self-reported stress, and anxiety levels were associated with the seizures.

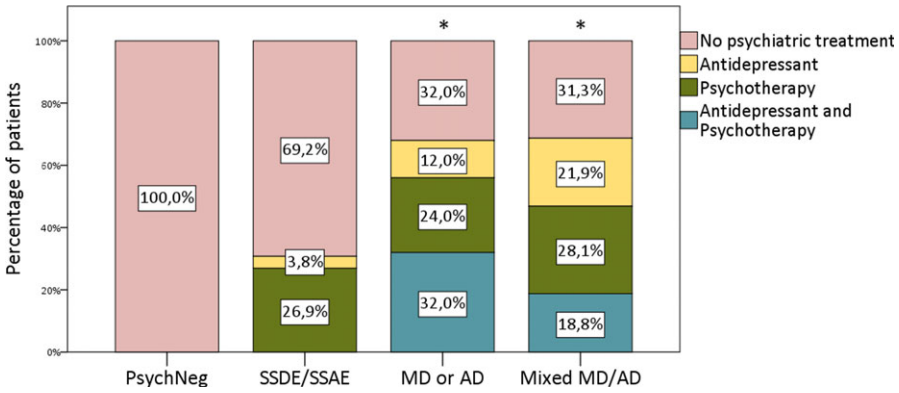

Figure 3.
Pharmacologic and nonpharmacologic psychiatric treatment according to psychiatric diagnosis groups. We observed that 31.6% of patients with a current diagnosis of depression and/or anxiety (*) were not receiving specific psychiatric treatment. PsychNeg, asymptomatic psychiatric symptoms; MD, mood disorders; AD, anxiety disorders; SSDE, subsyndromic forms of depressive episodes; SSAE, subsyndromic forms of anxiety episodes.

We observed that 18 patients (31.6%) with diagnoses of psychiatric disorders (G3 and G4), were receiving neither psychiatric pharmacologic nor nonpharmacologic treatment. Unfortunately, they had not been properly diagnosed earlier. The undertreatment and underdiagnosis of depression is not new in the literature, despite the high prevalence of psychiatric disorders in patients with epilepsy.[1,37] As detected in a cross-sectional study of 73 TLE patients, none of the 16 patients with current MDD were receiving psychiatric treatment.[1]

The recognition and treatment of psychiatric disorders in patients with epilepsy is essential, as depression, for example, is an independent predictor of increased suicidal risk, poor quality of life, greater medical costs associated with psychiatric treatment, higher use of health services,[37] and social disability.[38] Unfortunately, clinical manifestations of depression can be atypical[37] in PWE, preventing early detection especially by general physicians. In addition, active investigation of depressive and psychiatric symptoms is not routine for most of physicians who treat epilepsy. Furthermore, there are few options of validated instruments for diagnosis and screening of psychiatric disorders in epilepsy, and most of the doctors are not familiar with these instruments.[39] The NDDI-E appears to be an important tool for screening MDE, considering its simplicity and facility for application[17]; however, a more in-depth evaluation is recommended to verify the diagnosis and to check the existence of others psychiatric disorders and their duration.[9] We did not observe any differences among the patients with subsyndromic forms of depression and anxiety. Another possibility for classification of subsyndromes could be a positive NDDI-E and negative SCID-I, as the BDI could be artificially inflated by side effects of AEDs. However, the fact that all but two patients were using AEDs does not explain the differences among subgroups.

As important as the detection of symptoms, there are problems related to the negligence from patients, family members, and clinicians who have overlooked the psychiatric disorders in epilepsy,[40] thereby minimizing the relationship between MD, AD, and epilepsy. In some situations, psychiatric symptoms are considered "natural consequences of epilepsy," rather than comorbidities that deserve specific attention and treatment. We expect to raise awareness about the importance of diagnosing and treating psychiatric disorders, aiming to improve not only QoL, but also seizure control.

One limitation of our study is the lack of evaluation of QoL. This information would potentially contribute to deeper understanding of the impact of psychiatric disorders on the lives of these patients. Other possible limitations are related to the effects and interactions of the antidepressants, AEDs and psychotherapy in patients with psychiatric disorders, considering their dosage and duration. Unfortunately, we were not able to explore such interactions in details. Another limitation is the small sample sizes for some subgroups.

Conclusions

Depression and anxiety occurring together and a family psychiatric history are associated with pharmacoresistant seizures in patients with MTLE. Whether treatment of comorbid psychiatric disorders may impact seizure frequency is yet to be established.

Acknowledgments

The current study was supported by São Paulo Research Foundation (Grants 2014/08765-9 and 2011/21818-6) and National Council for Scientific and Technological Development, Brazil (Grants 140241/2012-4 and 130405/2011-6).

Disclosure

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal′s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Data S1. Supplementary methods (patients' selection, patients with a past psychiatric history excluded from the PsychNeg group, and MRI acquisition/procedures).

Table S1. Clinical and sociodemographic data from the 16 patients who were excluded from the group without current psychiatric symptoms.