An investigation into the psychosocial effects of the postictal state

Colin B. Josephson, MD,
MSc
Jordan D.T. Engbers,
PhD
Tolulope T. Sajobi, PhD
Nathalie Jette, MD, MSc
Yahya Agha-Khani, MD
Paolo Federico, MD, PhD
William Murphy, MD
Neelan Pillay, MBChB
Samuel Wiebe, MD, MSc

Correspondence to
Dr. Wiebe:
swiebe@ucalgary.ca

ABSTRACT

Objective: To determine whether postictal cognitive and behavioral impairment (PCBI) is independently associated with specific aspects of a patient's psychosocial health in those with epilepsy and nonepileptic events.

Methods: We used the University of Calgary's Comprehensive Epilepsy Clinic prospective cohort database to identify patients reporting PCBI. The cohort was stratified into those diagnosed with epilepsy or nonepileptic events at first clinic visit. Univariate comparisons and stepwise multiple logistic regression with backward elimination method were used to identify factors associated with PCBI for individuals with epilepsy and those with nonepileptic events. We then determined if PCBI was independently associated with depression and the use of social assistance when controlling for known risk factors.

Results: We identified 1,776 patients, of whom 1,510 (85%) had epilepsy and 235 had nonepileptic events (13%). PCBI was independently associated with depression in those with epilepsy (odds ratio [OR] 1.73; 95% confidence interval [CI] 1.06–2.83; $p = 0.03$) and with the need for social assistance in those with nonepileptic events (OR 4.81; 95% CI 2.02–11.42; $p < 0.001$).

Conclusions: PCBI appears to be significantly associated with differing psychosocial outcomes depending on the patient's initial diagnosis. Although additional research is necessary to examine causality, our results suggest that depression and employment concerns appear to be particularly important factors for patients with PCBI and epilepsy and nonepileptic attacks, respectively.

Neurology® 2016;86:723–730

GLOSSARY

AED = antiepileptic drug; **CEP** = Comprehensive Epilepsy Programme; **CI** = confidence interval; **DSM-IV** = *Diagnostic and Statistical Manual of Mental Disorders, 4th edition*; **OR** = odds ratio; **PCBI** = postictal cognitive and behavioral impairment.

The postictal state constitutes the period of time between termination of a seizure and return to the baseline level of function.¹ The patient may experience no neurologic dysfunction or may alternatively have mild, moderate, or severe levels of impairment of varying duration.

Confusion, fear, and agitation are the most frequently encountered symptoms during the postictal state.² These symptoms can be extremely debilitating^{3,4} and may last hours to days after a seizure.¹ However, there is a relative paucity of data related to the clinical, psychological, and social consequences of postictal cognitive and behavioral impairment (PCBI) in the current literature.

PCBI can persist for prolonged periods and may expose the patient to additional stigma, limit employment opportunities, and contribute to lowered self-esteem. Furthermore, employers may not wish to hire or retain people whose seizures do not simply terminate with a return to normal baseline but instead involve potentially prolonged periods of confusion and disorientation. These factors are reasonably expected to compound any preexisting disposition to adverse psychosocial outcomes.

It is our observation that in contrast to patients with immediate postictal recovery, those with PCBI seem more prone to fatigue and low mood. In the absence of existing evidence, we hypothesized a priori that PCBI would cause significant distress in excess of that related to the seizure itself.

Supplemental data
at Neurology.org

From the Department of Clinical Neurosciences (C.B.J., N.J., Y.A.-K., P.F., W.M., N.P., S.W.), Clinical Research Unit (J.D.T.E., T.T.S., S.W.), and Department of Community Health Sciences (T.T.S., N.J., S.W.), Cumming School of Medicine, Hotchkiss Brain Institute (T.T.S., N.J., P.F., S.W.), and O'Brien Institute of Public Health (T.T.S., N.J., S.W.), University of Calgary, Canada.

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

We explored this independently in patients diagnosed with epilepsy and nonepileptic events as it was anticipated that PCBI could differentially affect these 2 populations.

METHODS Study population. The Calgary Comprehensive Epilepsy Programme (CEP) collects data prospectively and systematically in a standardized manner on adult (aged 16 years and older) outpatients at their first and subsequent clinical encounters. The CEP serves a local population of over 1.2 million people and routinely receives local, provincial, and interprovincial referrals. All patients provide demographic, social, employment, and basic health-related information. The physician responsible for the patient collects additional data pertaining to seizure and epilepsy characteristics, medical and psychiatric history, physical examination findings, the results of diagnostic investigations such as EEG, video-EEG monitoring, and neuroimaging, multidisciplinary consults, antiepileptic drug (AED) use, and surgical history.

Prospective data collection started in 2007. Data were continuously added up until the date of analysis (October 2014). All results were documented prospectively in a standardized database. The cohort was stratified into those with epilepsy, those with nonepileptic events (including syncope, presyncope, migraines, anxiety or other psychiatric syndromes, drug-induced nonepileptic events, transient ischemic attacks, benign paroxysmal positional vertigo, psychogenic nonepileptic attacks, and unexplained symptoms), and those with concurrent epilepsy and nonepileptic events. The initial diagnosis was determined through a detailed patient history, physical examination, and review of antecedent imaging and ancillary testing such as prior routine and video-EEG telemetry results.

Study variables. There is no standardized or validated definition of PCBI. Hence, we defined it as any state of confusion or agitation in the postictal period that was noticeable to the patient or eyewitnesses and whose presence could be elicited through clinical history. Rather than splitting the condition into agitation or confusion, we combined the conditions as both were believed to have a similar deleterious effect on patient health and bystanders' perceptions of the patient's condition. It was assessed by multiple, overlapping approaches. Staff epileptologists comprehensively addressed the issue as a part of the patient's history and used ancillary history from the patient's family and any witnesses to the events where possible. Finally, available medical records were examined if this information was not available at the clinic visit. Physicians then indicated the presence or absence of PCBI on a standardized post-first visit questionnaire.

Depression was identified in a similar fashion. Staff epileptologists inquired as to whether the patient had ever received a formal diagnosis of depression. If not, they further explored the issue by asking directed questions based on DSM-IV⁵ criteria to determine if the patient was currently depressed or had symptoms consistent with prior depression that was missed or not reported by the patient to other physicians.

The need for social assistance was determined both through the clinical interview and through the patient questionnaire. Patients were asked to report their predominant means of income on the patient-reported questionnaire. Specifically, the patient was asked to indicate their primary source of income: employment, receiving income assistance through the Assured Income for the Severely Handicapped program (an Alberta provincial program that provides financial and health-related assistance to adults with

disability), social services income from another province, private disability insurance, or no income.

We identified epilepsy risk factors, etiology, seizure/event characteristics, seizure/event triggers, and medical comorbidities through a systematic neurologic history, physical examination, and results of ancillary investigations. We evaluated cigarette smoking, recreational drug use, and alcohol intake as binary outcomes defined by whether or not the patient regularly used ($\geq$ once per week) each substance. This information was provided both by the physician and the patient questionnaires. Current chronic medical condition was defined as any health issue that required current ongoing specialist medical management.

Statistical analysis. Parametric and nonparametric statistics were used where appropriate. We performed univariable comparisons (t tests and χ^2 exact tests) of continuous clinical and demographic variables between individuals with and without PCBI. We opted to use a conservative approach by limiting the analysis to only those variables deemed to be of clinical significance by study investigators (C.B.J., J.D.T.E., and S.W.). Spearman rank correlation was used to assess the presence of collinearity among independent variables. All statistical tests were conducted using 2-sided tests of statistical significance.

We then used a Bonferroni correction for multiple testing (between 20 and 25 comparisons; $\alpha^* \leq 0.002$) to control the overall type I error for the multiple comparisons. All variables retaining statistical significance were then included in backward stepwise elimination logistic regression. We used a significance threshold of 0.15 for removal and 0.10 for addition.⁶

If interictal depression or the need for social assistance was significantly associated with PCBI in any group, multiple logistic regression was used to determine whether the association retained significance when controlling for known risk and protective factors selected a priori. When evaluating depression, we controlled for age,⁷⁻⁹ sex,⁷⁻⁹ marital status,⁸ education level,^{8,9} employment status,^{10,11} use of social services,¹² the presence of a chronic medical comorbidity,¹⁰ occurrence of seizures over the prior year,¹³ epilepsy of presumed genetic origin,¹⁴ focal dyscognitive seizures,^{7,15} a temporal lobe focus,¹⁶ a frontal lobe focus,¹⁶ current AED use,^{10,16} and a history of epilepsy surgery.¹⁶ When evaluating the need for social assistance, we controlled for current age, age at event onset (no collinearity was detected between age at onset and current age), sex, level of education, marital status, regular use of recreational drugs, current or past diagnosis of depression, concurrent chronic medical comorbidities, and occurrence of any events over the prior year.

All statistical analyses were performed using Stata: Data Analysis and Statistical Software (version 13.0).¹⁷ Data imputation methods were not used due to the limited number of missing cases (at least 96% completeness of follow-up for clinical variables).

Standard protocol approvals, registrations, and patient consents. This analysis forms part of a Quality Improvement Project initiative approved by our local ethics review board (The University of Calgary's Conjoint Health Research Ethics Board). All patients (or guardians of patients) provided written informed consent. All data were collected, managed, stored, and extracted using REDCap electronic capture tools hosted at the University of Calgary's Clinical Research Unit.¹⁸

RESULTS We identified 1,776 patients who underwent a first evaluation at the CEP clinics. Of these patients, 1,510 (85%) were considered to only have epilepsy, 235 (13%) were considered to only have only nonepileptic events, and 31 (2%) were considered to have both. Our analyses focused on the subgroups

Table 1 Demographic and clinical characteristics of all first referrals to the Comprehensive Calgary Epilepsy Clinic

	Epilepsy only (n = 1,510)	Nonepileptic events (n = 235)	p Value
Female ^a	771/1,510 (51)	140/235 (60)	0.015
Age, y ^a	32 (21-50)	40 (26-51)	0.002
Age at onset, y ^a	18 (9-35)	31 (18-46)	<0.001
Epilepsy risk factors/etiology			
Birth trauma ^a	96/1,508 (6)	3/235 (2)	0.003
Developmental disorder ^a	193/1,508 (13)	11/235 (5)	0.001
Febrile convulsions ^a	120/1,507 (8)	5/235 (2)	0.003
CNS infection ^a	71/1,509 (5)	3/234 (1)	0.038
Head injury	392/1,509 (26)	67/234 (29)	0.675
Stroke	105/1,508 (7)	8/234 (3)	0.121
Family history of epilepsy	330/1,509 (22)	43/235 (18)	0.455
Seizure characteristics			
Seizures with aura	704/1,508 (47)	NA	NA
Generalized tonic-clonic seizures	1,176/1,509 (78)	NA	NA
Focal dyscognitive seizures	642/1,507 (43)	NA	NA
Focal nondyscognitive seizures	410/1,507 (27)	NA	NA
Seizure triggers			
Sleep deprivation	585/1,510 (39)	NA	NA
Concurrent illness	149/1,508 (10)	NA	NA
Flashing lights	175/1,506 (12)	NA	NA
Stress	632/1,508 (42)	NA	NA
Alcohol consumption	193/1,509 (13)	NA	NA
Seizure treatment			
Ever used an AED ^a	1,335/1,509 (88)	91/235 (39)	<0.001
Epilepsy surgery	66/1,508 (4)	NA	NA
Seizure-free in the last year	315/1,510 (21)	NA	NA
Current chronic medical condition ^a	549/1,510 (36)	110/235 (47)	0.002
Psychiatry referral ^a	158/1,506 (10)	39/234 (17)	0.006
Past or current depression ^a	287/1,510 (19)	60/235 (26)	0.020
Married/common-law/widowed ^a	635/1,502 (42)	120/233 (52)	0.008
High school or greater education	1,378/1,475 (93)	224/232 (97)	0.065
Currently employed	712/1,500 (47)	119/233 (51)	0.305
Requires social services	322/1,510 (21)	46/235 (20)	0.541
Social habits			
Regular alcohol use ^a	580/1,498 (39)	119/234 (51)	<0.001
Recreational drug use	135/1,494 (9)	18/233 (8)	0.513
Smokes cigarettes	339/1,499 (23)	58/234 (25)	0.462
Currently driving ^a	439/1,482 (30)	120/228 (53)	<0.001

Abbreviations: AED = antiepileptic drug; NA = not applicable.

The population is divided into those with only epilepsy and those with only nonepileptic events. Values are n (%) or median (interquartile range).

^aSignificant at $\alpha \leq 0.05$.

with only epilepsy and only nonepileptic events as the number of patients displaying both types of events was too small to draw any meaningful conclusions.

The majority of patients with epilepsy (1,089/1,510; 72%) and half the patients with nonepileptic events (118/235; 50%) reported PCBI. Those

diagnosed with epilepsy differed from those diagnosed with nonepileptic events on a number of demographic and clinical indices (table 1).

Epilepsy cohort. Table 2 displays the results of the associations between the presence of PCBI and 25 a priori selected demographic, clinical, diagnostic, and treatment variables. Using the Bonferroni correction, we identified 5 variables that were significantly associated with PCBI.

All 5 retained significance following backward stepwise elimination logistic regression. No collinearity was encountered (adjusted R^2 0.0784). Multiple logistic regression analysis of all 5 factors (c-statistic 0.68)

demonstrated that the odds of having PCBI were increased for those with generalized tonic-clonic seizures (odds ratio [OR] 3.45; 95% confidence interval [95% CI] 2.64–4.51; $p < 0.001$), those with an aura (OR 1.63; 95% CI 1.27–2.09; $p < 0.001$), those with depression (OR 1.47; 95% CI 1.05–2.05; $p = 0.022$), and those with a history of head injury (OR 1.38; 95% CI 1.07–1.78; $p = 0.012$), and decreased for those who were still permitted to drive (OR 0.72; 95% CI 0.55–0.93; $p = 0.013$; figure e-1 on the *Neurology*[®] Web site at www.neurology.org).

Since depression was found to be independently associated with PCBI in those with epilepsy, we next sought to determine whether PCBI independently

Table 2 Univariable comparisons and associated odds ratios (95% CI) for the occurrence of PCBI in the subgroup with only epilepsy

	No PCBI (n = 421)	PCBI (n = 1,089)	Odds ratio (95% CI)	p Value
Female	223/421 (53)	548/1,089 (50)	0.90 (0.71–1.13)	0.356
Age, y	33 (21–54)	33 (21–49)	NA	0.135
Age at onset, y	19 (10–39)	18 (9–34)	NA	0.265
Epilepsy risk factors/etiology				
Developmental disorder	47/420 (11)	146/1,088 (13)	1.15 (0.86–1.55)	0.317
Febrile convulsions	34/419 (8)	86/1,088 (8)	1.20 (0.94–1.53)	0.132
CNS infection	15/420 (4)	56/1,089 (5)	1.10 (0.80–1.51)	0.546
Head injury ^a	81/420 (19)	311/1,089 (29)	1.46 (1.14–1.86)	0.002
Brain tumor	24/420 (6)	40/1,087 (4)	0.64 (0.46–0.91)	0.011
Encephalomalacia	22/316 (7)	87/803 (11)	1.62 (1.0–2.78)	0.050
Family history of epilepsy	78/420 (19)	252/1,089 (23)	1.30 (1.03–1.64)	0.023
Seizure characteristics				
Seizures with aura ^a	164/421 (39)	531/1,087 (49)	1.50 (1.19–1.88)	0.001
Generalized tonic clonic seizures ^a	259/420 (62)	917/1,089 (84)	3.31 (2.56–4.28)	<0.001
Focal dyscognitive seizures	168/419 (40)	474/1,088 (44)	1.15 (0.91–1.45)	0.222
Focal nondyscognitive seizures	133/419 (32)	277/1,088 (25)	0.73 (0.57–0.94)	0.014
Seizure treatment				
Ever used an AED	359/421 (85)	976/1,088 (90)	1.50 (1.07–2.10)	0.016
Epilepsy surgery	18/420 (4)	48/1,088 (4)	0.90 (0.59–1.38)	0.650
Seizure-free in the last year	103/421 (24)	212/1,089 (19)	0.74 (0.57–0.98)	0.032
Current chronic medical condition	144/421 (34)	405/1,089 (37)	1.13 (0.89–1.44)	0.279
Past or current depression ^a	59/421 (14)	228/1,089 (21)	1.62 (1.18–2.22)	0.002
Married/common-law/widowed	196/417 (47)	439/1,085 (40)	0.76 (0.61–0.96)	0.022
Requires social services	76/421 (18)	246/1,089 (23)	1.32 (0.99–1.76)	0.054
Social habits				
Regular alcohol use	162/415 (39)	418/1,083 (39)	0.98 (0.77–1.24)	0.876
Recreational drug use	27/413 (6)	108/1,081 (10)	0.35 (1.02–2.46)	0.037
Smokes cigarettes	76/416 (18)	263/1,083 (24)	1.43 (1.07–1.91)	0.013
Currently driving ^a	143/405 (35)	296/1,077 (27)	0.69 (0.54–0.89)	0.002

Abbreviations: AED = antiepileptic drug; CI = confidence interval; NA = not applicable; PCBI = postictal cognitive and behavioral impairment.

Values are n (%) or median (interquartile range).

^aSignificant at $\alpha^* \leq 0.002$.

predicts depression. When controlling for known risk and protective factors, PCBI was independently associated with depression (OR 1.73; 95% CI 1.06–2.83; $p = 0.03$) in a multivariable logistic regression analysis (c-statistic 0.7972; figure 1). No collinearity was encountered. In addition to PCBI, having a concurrent chronic medical comorbidity (OR 10.8; 95% CI 6.6–17.8; $p < 0.001$), female sex (OR 2.36; 95% CI 1.52–3.65; $p < 0.001$), achieving a completed high school or greater education (OR 1.71; 95% CI 1.30–7.99; $p = 0.01$; this may be secondary to lost opportunities that are usually proportionate to the level of education achieved), and advancing age (OR for each year 1.01; 95% CI 1.00–1.03; $p = 0.02$) were all associated with increased odds of depression.

Nonepilepsy cohort. Table 3 displays the results of the associations between the presence of PCBI and 20 a priori selected demographic, clinical, and treatment variables. Using the Bonferroni correction, we identified 2 variables (a history of head injury and need for social assistance) that were significantly associated with PCBI. We did not pursue backward stepwise elimination logistic regression given that we only identified 2 variables that retained significance.

We next sought to determine whether PCBI was independently associated with the need for social services when controlling for potential covariables identified through clinical experience (figure 2). The presence of PCBI was independently associated with the use of social assistance in a multivariable logistic regression model (OR 5.12; 95% CI 2.16–12.11;

$p < 0.001$). In addition, depression (OR 2.77; 95% CI 1.11–6.93; $p = 0.029$) was also associated with increased odds of needing social assistance, while being in a relationship (OR 0.21; 95% CI 0.08–0.55; $p = 0.001$) and female sex (OR 0.39; 95% CI 0.17–0.89; $p = 0.025$) were both associated with decreased odds. No collinearity was encountered (c-statistic 0.8157).

DISCUSSION Patients attending tertiary care epilepsy clinics frequently report PCBI irrespective of whether they have epilepsy (72%) or nonepileptic events (50%). In this analysis of factors captured during the patient's first evaluation in a cohort study of adult referrals to a regional tertiary care epilepsy center, the presence of PCBI was differentially associated with worse psychosocial outcomes depending on the patient's initial diagnosis of epilepsy or nonepileptic events.

There appears to be a bidirectional relationship between epilepsy and depression¹⁹ suggesting common pathophysiologic processes underlying both diseases.²⁰ The specific mechanisms responsible for the postictal period, irrespective of its manifestation, may predispose the patient to interictal depression. Alterations in acetylcholine, serotonin, opiates, adenosine, and nitric oxide have all been reported during the postictal state.²¹ This could account for the fact that patients with interictal depression can experience acute exacerbations during the postictal period and may explain why the characteristics of major depression are often atypical in patients with epilepsy.¹⁶

Figure 1 Odds ratio of depression according to postictal cognitive and behavioral impairment (PCBI) status when controlling for variables selected a priori from the literature

AED = antiepileptic drug; CI = confidence interval.

Table 3 Univariable comparisons and associated odds ratios (95% CI) for the occurrence of PCBI in the subgroup with only nonepileptic attacks

	No PCBI (n = 117)	PCBI (n = 118)	Odds ratio (95% CI)	p Value
Female	70/117 (60)	70/118 (60)	0.98 (0.58-1.65)	0.937
Age, y	42 (24-52)	40 (28-51)	NA	0.919
Age at onset, y	30 (17-47)	32 (20-45)	NA	0.926
Epilepsy risk factors/etiology				
Developmental disorder	5/117 (4)	6/118 (5)	1.20 (0.35-4.05)	0.769
Febrile convulsions	3/117 (3)	2/118 (2)	—	0.839
CNS infection	0/116 (0)	3/118 (3)	1.10 (0.80-1.51)	0.546
Head injury ^a	21/116 (18)	46/118 (39)	2.89 (1.58-5.27)	0.001
Brain tumor	2/117 (2)	2/117 (2)	1.00 (0.13-7.22)	1.000
Encephalomalacia	3/88 (3)	0/89 (0)	0.0 (0.0-1.25)	0.079
Family history of epilepsy	25/117 (21)	18/118 (15)	0.66 (0.33-1.29)	0.227
Event treatment				
Ever used an AED	37/117 (32)	54/118 (46)	1.82 (1.07-3.11)	0.027
Event-free in the last year	17/117 (15)	10/118 (8)	0.54 (0.23-1.25)	0.150
Current chronic medical condition	47/117 (40)	63/118 (53)	1.70 (1.01-2.86)	0.043
Past or current depression	21/117 (18)	39/118 (33)	2.25 (1.22-4.14)	0.009
Married/common-law/widowed	63/116 (54)	57/117 (49)	0.79 (0.47-1.34)	0.393
Requires social services ^a	10/117 (9)	36/118 (31)	4.70 (2.02-10.0)	<0.001
Social habits				
Regular alcohol use	66/116 (57)	53/118 (45)	0.62 (0.36-1.03)	0.067
Recreational drug use	5/115 (4)	13/118 (11)	2.72 (0.93-7.9)	0.065
Smokes cigarettes	25/116 (22)	33/118 (28)	1.41 (0.77-2.56)	0.257
Currently driving	69/114 (61)	51/114 (45)	0.53 (0.31-0.89)	0.017

Abbreviations: AED = antiepileptic drug; CI = confidence interval; NA = not applicable; PCBI = postictal cognitive and behavioral impairment.

Values are n (%) or median (interquartile range).

^aSignificant at $\alpha^* \leq 0.002$.

Depression and neurovegetative states are common postictal symptoms, affecting up to 46% and 62% of patients with epilepsy, respectively.²² We cannot rule out the possibility that patients with immediate postictal depression are being inadvertently diagnosed with major depressive disorder. PCBI is common; it was present in 72% of our cohort with epilepsy and has been reported in up to 88% of patients with drug-resistant focal epilepsy.²² However, although postictal depression may mimic major depressive disorder, it typically does not fulfil the DSM-IV criterion for time (symptoms persisting for at least 2 weeks), thus making this possibility less likely.^{23,24} The likelihood of a misdiagnosis was further minimized by comprehensive exploration of the patient's history at the initial clinic visit.

We performed a separate analysis to determine whether the effects of PCBI were consistent in patients with nonepileptic events. Although not meant as a control group, and acknowledging that this group

rather represents a distinct subgroup of disparate disease processes, our results indicate that PCBI does appear to affect the psychosocial health of those with nonepileptic events, though in a differential fashion. This suggests that periods of disorientation, confusion, aggression, or psychiatric disturbances may interfere with the patient's ability to acquire gainful employment that provides sufficient remuneration to permit independent living. Our study was not designed to examine the root causes of this association. Additional factors, such as a history of abuse or physical or psychological trauma, may also be influential and should be explored in future studies. Despite this, it is feasible that employers are reluctant to hire individuals who experience postevent periods of neuropsychological dysfunction due to the potential effect on productivity or perceived liability for work-related injury. That this association was not observed in those with epilepsy may be attributed to the fact that additional epilepsy-specific factors were sufficiently strong

Figure 2 Odds ratio of social assistance as the primary income source according to postictal cognitive and behavioral impairment (PCBI) when controlling for variables selected a priori

CI = confidence interval.

to outweigh the independent influence of the postictal state on the requirement for social assistance. Ultimately, in spite of the heterogeneous nature of this group, a strong statistical association between PCBI and the need for social assistance was demonstrated and thus warrants further exploration.

Our study has benefitted from its position as a local tertiary care referral center. Data were provided both by patients and 6 epileptologists, thus permitting checks for internal consistency. Standardized questionnaires and a systematic, prospective collection of data have enabled consistent application of predetermined definitions for study variables. This has enhanced accuracy of reporting and has ensured near complete collection of data. The overall sample size (1,776 patients) meant that a sufficient number of outcomes were encountered to facilitate an extensive analysis of factors associated with the postictal state. We additionally used a Bonferroni correction and employed backward stepwise elimination logistic regression to limit the potential for type I error.

The design of this study, however, precludes our ability to establish a cause-effect relationship between the exposures and outcome. Patients were recruited at their first epilepsy clinic visit rather than at a specific point in the natural history of their disease. Thus, patients without antecedent neuroimaging or EEG testing (routine or video-EEG telemetry) may have been misclassified as having epileptic seizures or nonepileptic events. Furthermore, we cannot determine whether the existence of a postictal state directly preceded the development of depression or the need for social assistance. We could not characterize PCBI, such as describing the frequency, duration, and severity of the symptoms, both due to the limitations of the questionnaires in which the data from the patient's history were recorded and the lack of standardized, evidence-based criteria for

evaluating this condition. The lack of a validated definition meant that we had to define it as a dichotomous outcome. However, the 6 epileptologists in the clinic work closely together, thus fostering homogeneity of practice that should enhance reliability of response to this question. Depression was defined using clinical criteria based on DSM-IV but future iterations of the study will also include validated depression rating scales such as the Patient Health Questionnaire-9 Depression scale²⁵ to assess specific symptoms of depression.

We also cannot exclude selection bias since our cohort of patients is derived from a tertiary care referral center. It is challenging to attribute our results to differential recruitment based on their exposures and outcomes of interest. Despite multiple overlapping means of diagnosing depression, we still anticipate a degree of reporting error. However, this would not be expected to differ on account of a postictal state and instead, nondifferential misclassification bias is anticipated that would dilute the magnitude of our point estimate. Response bias may play a role in those with nonepileptic events. In their attempts to seek help, they may be more prone to admitting the need for social assistance; however, this is a highly regulated process and it is unlikely that many would qualify for this program if they were simply malingering. We cannot rule out the effects of residual confounding though the power of our study enabled us to control for known independent risk and protective factors identified a priori. Finally, the external validity of our study may be limited by the referral source. The potential for overrepresentation of patients with more severe PCBI must be considered when interpreting the results. Future studies, potentially involving patients admitted to video-EEG telemetry units, will permit an investigation into whether the severity of PCBI influences the risk of depression. Additionally, population-based studies are

required to verify that our results are applicable to general patients with epilepsy and nonepileptic events.

There appears to be a differential association between PBCI and psychosocial outcomes based on the patient's diagnosis. Although additional research is required to establish causality, our results suggest that depression may be particularly important for patients with epilepsy and PCBI, while employment is a significant source of concern for patients with nonepileptic events and PCBI. Future recruitment and incorporation of our longitudinal follow-up data will permit more definitive conclusions regarding causality. Additional studies identifying predictors of a lack of PCBI could also be insightful. Furthermore, additional studies formally defining PCBI are critical and should be pursued to set the foundation for studies of direct causality. These associations appear strong enough, however, to warrant specific inquiry and intervention for patients attending tertiary care epilepsy clinics.

AUTHOR CONTRIBUTIONS

C.B.J., J.D.T.E., T.T.S., and S.W. contributed to the design of the study. C.B.J., J.D.T.E., and T.T.S. performed the analyses. C.B.J. prepared the initial draft of the manuscript and C.B.J., J.D.T.E., T.T.S., N.J., Y.A.-K., P.F., W.M., N.P., and S.W. contributed to the revising of the manuscript. C.B.J., J.D.T.E., T.T.S., N.J., Y.A.-K., P.F., W.M., N.P., and S.W. agree to the publication of this version of the manuscript.

STUDY FUNDING

No targeted funding reported.

DISCLOSURE

C. Josephson is the recipient of an American Brain Foundation/American Epilepsy Society/Epilepsy Foundation/American Academy of Neurology Susan S. Spencer Clinical Research Training Fellowship in Epilepsy and an Alberta Innovates: Health Solutions Clinician Fellowship. J. Engbers is funded by an Alberta Innovates: Health Solutions Postgraduate Fellowship. T. Sajobi is funded by the University of Calgary New Investigators' Seed Grant. N. Jette is the holder of a Canada Research Chair in Neurological Health Services Research and an Alberta Innovates Health Solutions Population Health Investigator Award. She is also on the editorial board of *Neurology*. Y. Agha-Khani, P. Federico, W. Murphy, and N. Pillay report no disclosures relevant to the manuscript. S. Wiebe is the holder of the Hopewell Professorship for Clinical Neurosciences Research at the Hotchkiss Brain Institute, University of Calgary. Go to Neurology.org for full disclosures.

Received June 7, 2015. Accepted in final form October 28, 2015.

REFERENCES

1. Fisher RS, Engel JJ Jr. Definition of the postictal state: when does it start and end? *Epilepsy Behav* 2010;19:100–104.
2. Widdess-Walsh P, Devinsky O. Historical perspectives and definitions of the postictal state. *Epilepsy Behav* 2010;19:96–99.
3. Kanemoto K, Kawasaki J, Mori E. Violence and epilepsy: a close relation between violence and postictal psychosis. *Epilepsia* 1999;40:107–109.
4. Krauss G, Theodore WH. Treatment strategies in the postictal state. *Epilepsy Behav* 2010;19:188–190.
5. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 4th ed. Washington, DC: American Psychiatric Association; 1994.

6. Riffenburgh RH. Multiple and Curvilinear Regression, 3rd ed. San Diego: Elsevier; 2012.
7. Peng WF, Ding J, Li X, Mao LY, Wang X. Clinical risk factors for depressive symptoms in patients with epilepsy. *Acta Neurol Scand* 2014;129:343–349.
8. Coryell W, Endicott J, Keller M. Major depression in a nonclinical sample: demographic and clinical risk factors for first onset. *Arch Gen Psychiatry* 1992;49:117–125.
9. Blazer DG, Kessler RC, McGonagle KA, Swartz MS. The prevalence and distribution of major depression in a national community sample: the National Comorbidity Survey. *Am J Psychiatry* 1994;151:979–986.
10. Kui C, Yingfu P, Chenling X, Wenqing W, Xiuhua L, Di S. What are the predictors of major depression in adult patients with epilepsy? *Epileptic Disord* 2014;16:74–79.
11. Wang JL, Schmitz N, Dewa CS. Socioeconomic status and the risk of major depression: the Canadian National Population Health Survey. *J Epidemiol Community Health* 2010;64:447–452.
12. Reisinger EL, Dilorio C. Individual, seizure-related, and psychosocial predictors of depressive symptoms among people with epilepsy over six months. *Epilepsy Behav* 2009;15:196–201.
13. Friedman DE, Kung DH, Laowattana S, Kass JS, Hrachovy RA, Levin HS. Identifying depression in epilepsy in a busy clinical setting is enhanced with systematic screening. *Seizure* 2009;18:429–433.
14. Indaco A, Carrieri PB, Nappi C, Gentile S, Striano S. Interictal depression in epilepsy. *Epilepsy Res* 1992;12:45–50.
15. Grabowska-Grzyb A, Jedrzejczak J, Naganska E, Fiszler U. Risk factors for depression in patients with epilepsy. *Epilepsy Behav* 2006;8:411–417.
16. Kanner AM. Depression in epilepsy: prevalence, clinical semiology, pathogenic mechanisms, and treatment. *Biol Psychiatry* 2003;54:388–398.
17. Stata Statistical Software: Release 13 [computer program]. College Station, TX: StataCorp; 2013.
18. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap): a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009;42:377–381.
19. Hesdorffer DC, Ishihara L, Mynealli L, Webb DJ, Weil J, Hauser WA. Epilepsy, suicidality, and psychiatric disorders: a bidirectional association. *Ann Neurol* 2012;72:184–191.
20. Kanner AM. Depression and epilepsy: a bidirectional relation? *Epilepsia* 2011;52:21–27.
21. Fisher RS, Schachter SC. The postictal state: a neglected entity in the management of epilepsy. *Epilepsy Behav* 2000;1:52–59.
22. Kanner AM, Soto A, Gross-Kanner H. Prevalence and clinical characteristics of postictal psychiatric symptoms in partial epilepsy. *Neurology* 2004;62:708–713.
23. Kanner AM, Trimble M, Schmitz B. Postictal affective episodes. *Epilepsy Behav* 2010;19:156–158.
24. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 5th ed. Washington, DC: American Psychiatric Association; 2013.
25. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med* 2001;16:606–613.