Epilepsy, Suicidality, and Psychiatric Disorders: A Bidirectional Association

Dale C. Hesdorffer, PhD,[1] Lianna Ishihara, PhD,[2] Lakshmi Mynepalli, MSc,[3] David J. Webb, MSc,[4] John Weil, MD,[5] and W. Allen Hauser, MD[1,6]

Objective: A study was undertaken to determine whether psychiatric disorders associated with suicide are more common in incident epilepsy than in matched controls without epilepsy, before and after epilepsy diagnosis.
Methods: A matched, longitudinal cohort study was conducted in the UK General Practice Research Database. A total of 3,773 cases diagnosed with epilepsy between the ages of 10 and 60 years were compared to 14,025 controls matched by year of birth, sex, general practice, and years of medical records before the index date. We examined first diagnosis of psychosis, depression, anxiety, and suicidality in each of the 3 years before and after the index date and annual prevalence of suicide. Referent diagnoses were eczema and acute surgery. The incidence rate ratio (IRR) was calculated for each year in the study period; the prevalence ratio (PR) was calculated for suicidality.
Results: The IRR of psychosis, depression, and anxiety was significantly increased for all years before epilepsy diagnosis (IRR, 1.5–15.7) and after diagnosis (IRR, 2.2–10.9) and for suicidality before epilepsy diagnosis (IRR, 3.1–4.5) and 1 year after diagnosis (IRR, 5.3). The PR was increased for suicide attempt before epilepsy onset (PR, 2.6–5.2) and after onset (PR, 2.4–5.6). Eczema and acute surgery were both associated with epilepsy in the first and third year after diagnosis.
Interpretation: Epilepsy is associated with an increased onset of psychiatric disorders and suicide before and after epilepsy diagnosis. These relations suggest common underlying pathophysiological mechanisms that both lower seizure threshold and increase risk for psychiatric disorders and suicide.

ANN NEUROL 2012;72:184–191

In January 2008 the US Food and Drug Administration issued an alert to health care providers warning of increased risk of suicidal thoughts and behaviors related to antiepileptic drugs (AEDs) based on data from a meta-analysis of 199 clinical trials.[1] This has prompted renewed interest in the association between epilepsy itself and psychiatric disorders, including suicidality.[2] Most previous studies are cross-sectional and limited to associations in patients with diagnosed epilepsy; some are in select populations from epilepsy centers, with resulting over-representation of complex partial seizures refractory to medication. When prediagnosis associations have been examined, major depression,[3–6] bipolar disorder,[4] and attempted suicide[4] have been associated with an increased risk for developing epilepsy. Recent studies also show that a psychiatric history before the onset of epilepsy increases the risk for continued seizures,[7,8] suggesting that premorbid psychiatric disorders may lower seizure threshold. The reciprocal relation between psychiatric disorders and epilepsy has not been examined.

We undertook a matched, longitudinal cohort study to determine the associations with psychiatric comorbidities in patients both before and after the diagnosis of epilepsy.

Subjects and Methods

The UK General Practice Research Database (GPRD) contains detailed information on diagnoses, prescriptions, investigations, risk factors, outcomes, and hospital referrals, together with basic demographic information for a sample of approximately 6.4

View this article online at wileyonlinelibrary.com. DOI: 10.1002/ana.23601

Received Jun 14, 2011, and in revised form Feb 11, 2012. Accepted for publication Mar 23, 2012.

Address correspondence to Dr Hesdorffer, GH Sergievsky Center, Columbia University, 630 West 168th Street, P & S Unit 16, New York, NY 10032. E-mail: dch5@columbia.edu

Current address for Dr Weil: Novartis Vaccines and Diagnostics, Hullenbergweg, Amsterdam, the Netherlands.

From the [1]Gertrude H. Sergievsky Center and Department of Epidemiology, Columbia University, New York, NY; [2]Worldwide Epidemiology, GlaxoSmithKline, Stockley Park, London, United Kingdom; [3]GlaxoSmithKline Pharmaceuticals Limited, Bangalore, India; [4]Observational Data Analytics, GlaxoSmithKline, Stockley Park, London, United Kingdom; [5]Worldwide Epidemiology, GlaxoSmithKline, New Frontiers Science Park (South), Harlow, United Kingdom; and [6]Department of Neurology, Columbia University, New York, NY.

Additional supporting information can be found in the online version of this article.

million people from >480 general practices throughout the United Kingdom from 1990 through 2008. Approximately 3.5 million people from 437 practices were active in the database at the time of analysis. The data are drawn from the computer systems used by general practitioners (GPs) to maintain the clinical records within their practices, and contain all records deemed relevant to patient care. Data quality is monitored continuously by the UK Medicines and Healthcare Regulatory Agency, and practices that fail to maintain the required standards are removed. The completeness and accuracy of the recording have been validated externally.[9] The database is population-based and representative of the age, sex, and geographic regions of the United Kingdom,[10] hence results are broadly applicable to the wider UK population.

Study Population

The GPRD database was used to identify cases with newly diagnosed (incident) epilepsy and controls without a history of epilepsy, using all available patient history prior to enrollment in the GPRD until December 31, 2008.

CASES. Cases aged 10 through 60 years with incident epilepsy were included if they had at least 1 epilepsy GPRD medical code recorded between 1993 and 2005, plus at least 2 AED prescriptions from 1 month before to 6 months after the epilepsy code was recorded (the index date).

CONTROLS. Four patients without a diagnosis of epilepsy at any time before the case's index date, even before GPRD entry, were randomly selected and matched to each case by age at the epilepsy index date, sex, GP practice, and duration of GPRD medical records prior to the index date. Consistent with incidence density sampling, qualifying controls were included who later developed epilepsy 3 or more years after their control index date.

Both cases and controls were required to have at least 3 years of full records prior to incident epilepsy and at least 1 day of history after epilepsy onset. Additionally, cases and controls had at least 1 GPRD medical or drug code for a condition other than epilepsy in the period 6 months before the index date to ensure that they were actively seeking care around the index date.

The lower limit of 10 years for incident epilepsy was selected rather than a younger age, because suicide and the psychiatric disorders studied would otherwise be extremely rare during the follow-up interval.[11] The upper age limit of 60 years for incident epilepsy was selected to minimize misclassification of epilepsy in the elderly, arising because direct medical record review is not possible. One example of such misclassification in the elderly would be inclusion of people prescribed antiepileptic drugs after acute symptomatic seizures associated with insults such as stroke to decrease the likelihood of later unprovoked seizures.

The study period was from 3 years before to 3 years after the index date.

Outcomes

Clinical data are currently recorded in primary care using Clinical Terms version 3 terminology (Read terms). Historical data that were recorded as OXMIS (Oxford Medical Information Systems) codes, based upon the International Classification of Disease and Office of Population and Census Statistics operation codes, have also been translated into equivalent Read codes on the GPRD. These GPRD medical codes were used to identify incident major depression, anxiety, substance abuse and dependence (including alcohol, drugs, and illicit drugs), suicidality, and psychosis (schizophrenia, mania, bipolar disorder, reactive psychosis, and other nonorganic psychoses). A diagnosis of bipolar disorder was included in the presence of manic or hypomanic episodes. When codes were present before the study period, even before GPRD entry, diagnoses during the study period were considered prevalent or recurrent. Suicidality included codes for attempted suicide and completed suicide; only suicide attempt was considered before epilepsy onset. The psychiatric outcomes were examined individually and in the aggregate as all psychiatric disorders.

We examined acute surgery and eczema as reference comorbidities to assess whether associations observed were specific to psychiatric disorders. Supplementary Tables 1 and 2 present both eczema and acute surgery. Acute surgery included appendectomy, emergency gall bladder surgery, and other emergency surgeries.

Coding lists used to identify comorbidities of interest were reviewed by 2 GlaxoSmithKline clinicians and W.A.H.

Statistical Analysis

Data were analyzed with SAS (SAS Institute, Cary, NC). For each comorbidity, we calculated the incidence rate (IR) in each year of the study period. The number of cases or controls with a new diagnostic code for an outcome was divided by the sum of case or control person-time in each time period. Subjects with a record of the specific comorbidity before the study period were excluded from the analysis of that comorbidity. For each ensuing time interval, subjects were excluded if they were diagnosed with the incident comorbidity in a previous time interval. Additionally, subjects lost to follow-up during the study period were not included in the following time period's analysis, leaving the risk set, which had to include at least 1 case and 1 control at the start of each time period. Person-time was calculated within each time period as the time to incident comorbidity, end of follow-up within the time period, or the end of the time period. Comorbidity diagnoses occurring on the same day as the index date were counted in the 1 year before the index date time period.

The IR ratio (IRR) was calculated by dividing the IR for cases by the IR for controls for each year in the study period. The IRR was calculated with 95% confidence intervals (CIs).[12]

We also calculated the annual prevalence of suicide in each year of the study period. The number of cases or controls with a first or recurrent diagnostic code during each year of observation was divided by the midpoint population for that year

TABLE: Descriptive Data on Cases with Incident Epilepsy and Matched Controls

Factors	Cases, n = 3,773	Controls, n = 14,025
Mean age at study entry, yr	37 ± 15	37 ± 15
Males	50.0%	50.0%
Idiopathic/cryptogenic epilepsy	88%	NA
Median GPRD follow-up, yr (IQR)	13.6 (9.8–18.0)	14.4 (10.8–18.6)
Median follow-up in the study, yr (IQR)	6.0 (6.0–6.0)	6.0 (6.0–6.0)

GPRD = General Practice Research Database; IQR = interquartile range; NA = not applicable.

for cases and controls. The prevalence ratio (PR) was calculated by dividing the annual prevalence of suicide for cases by the annual prevalence for controls for each year in the study period. The PR was calculated with 95% CIs.[12]

Analyses were repeated excluding all cases with a history of secondary causes of epilepsy (ie, stroke, traumatic brain injury), because psychiatric disorders are known to be associated with some of these conditions.

The same exclusions were applied to the matched control group. All authors contributed to the analysis; programming was performed by L.M.

Ethics Approval

We obtained approval from the Independent Scientific Advisory Committee for Medicines and Heathcare Products Regulatory Agency.

Results

Among 3,773 cases with epilepsy and 14,025 controls, mean age at study entry was 37 years for cases and controls, and 50% of cases and controls were male (Table). Median GPRD follow-up was 13.6 years for cases (interquartile range [IQR], 9.8–18.0) and 14.4 years for controls (IQR, 10.8–18.6). Among cases and controls, 20% were 10 to 19 years of age at incident epilepsy or the index date. The median follow-up during the study period was 6.0 years for cases and controls. Among cases, 84% had idiopathic/cryptogenic epilepsy.

Among the comorbidities that occurred prior to the study period, the most common was eczema, occurring in 19.0% of cases and of controls, followed by anxiety (18.5% in cases, 13.8% in controls) and depression (17.5% in cases, 11.7% in controls). Less common were bipolar disorder, psychosis, and suicidality, which occurred in 0.8 to 5.4% of cases and in 0.1 to 2.4% of controls before the study period. Incident psychiatric comorbidities were diagnosed on the index date in 8 cases (0.2%) and 5 controls (0.03%).

The IRR was significantly increased before and after epilepsy onset for depression, anxiety, bipolar disorder, and psychosis, as well as for incident suicidality. The IRR was statistically significantly increased for all years before and after epilepsy onset for psychiatric disorders in the aggregate (Supplementary Fig 1), for psychosis (Fig 1), and for depression (Fig 2). For substance abuse and dependence, anxiety, and suicidality, the IRR was significantly increased for all 3 years before and for the 2 years after epilepsy onset (Figs 3–5). The IRR for the referent comorbidities was not statistically significantly increased for most years, but was for acute surgery in the third year after epilepsy onset, and for eczema in the first year after epilepsy onset (see Supplementary Table 1). The annual prevalence of suicidality was significantly increased in each year before (PR, 2.6–5.2) and after epilepsy onset (PR, 2.4–5.6; Fig 6). After epilepsy onset, 40 of the 264 suicide attempts or completions in cases (15.2%) represented recurrence of suicide attempts from the preindex period, compared to 16 of 407 in controls (4.2%; $p < 0.0001$). Among the postindex suicide attempts or completions, 41.7% were recurrences in cases, and 17.9% were recurrences for controls ($p = 0.0003$).

Secondary analysis excluded pre-existing secondary causes of epilepsy from the case (n = 959 excluded) and control groups (n = 1,488 excluded). Pre-existing secondary causes included cerebral anoxia, cerebral palsy, central nervous system (CNS) infection, congenital brain malformations, dementia, head injury, hereditary degenerative disease, stroke, metabolic CNS disorders, multiple sclerosis, neurocysticercosis, neurosyphilis, other degenerative disease, and stroke. The secondary analysis included 2,793 cases and 9,390 controls, after applying the exclusions and deleting case–control sets for which there were either no cases or no controls remaining. In subsequent analyses limited to epilepsy of unknown etiology, the same magnitude and pattern of the increased rate for each incident psychiatric disorder and suicidality before and after epilepsy onset were observed (see Supplementary Table 2). The association with eczema and with acute surgery remained unchanged. In another analysis, excluding the secondary causes of epilepsy and substance

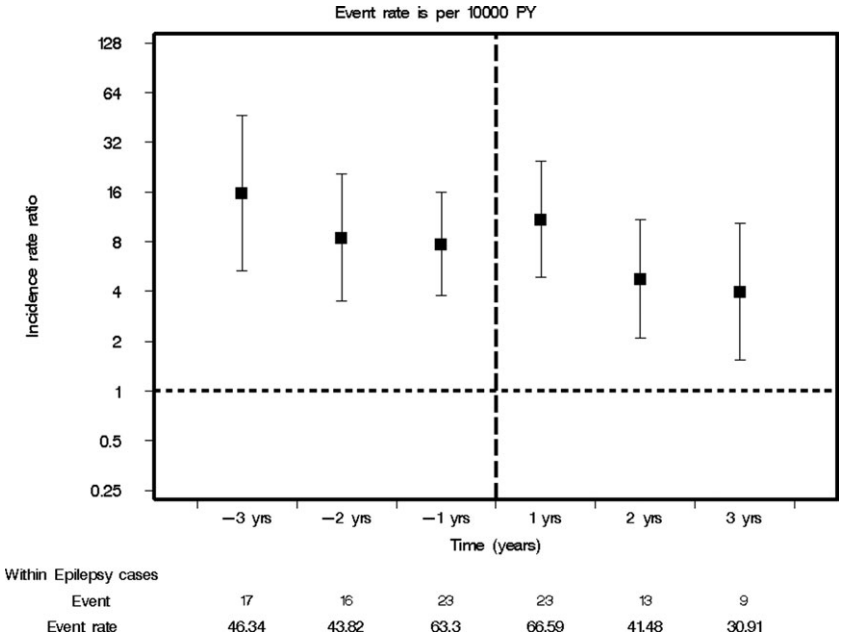

FIGURE 1: Trends in the incidence rate ratio for epilepsy versus controls with 95% confidence intervals for psychosis in the 3 years before and 3 years after epilepsy diagnosis. PY = person-years.

abuse and dependence, the relation between psychiatric disorders and epilepsy was unchanged (Supplementary Fig 2). Substance abuse and dependence remained associated with epilepsy after exclusion of secondary causes of epilepsy (see Supplementary Table 2).

Discussion

Psychiatric comorbidities are present in a substantial proportion of people with diagnosed epilepsy.[13–15] Historically, these comorbidities have been considered complications of the seizure disorder, resulting from a reaction to having epilepsy and to a loss of locus of control.[16,17] Recent epidemiologic studies have established a more complex relation between psychiatric disorders and epilepsy.[4–8,18–20] These studies show that a history of major depression[4–6,21] and bipolar disorder[4] are associated with an increased risk for developing epilepsy, risk for a first diagnosis of schizophrenia[19] is increased after the

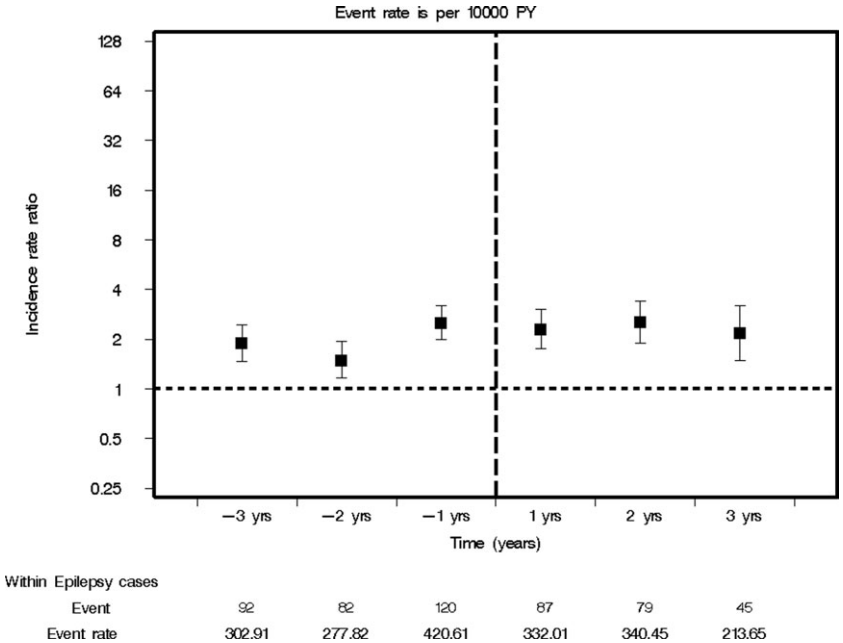

FIGURE 2: Trends in the incidence rate ratio for epilepsy versus controls with 95% confidence intervals for depression in the 3 years before and 3 years after epilepsy diagnosis. PY = person-years.

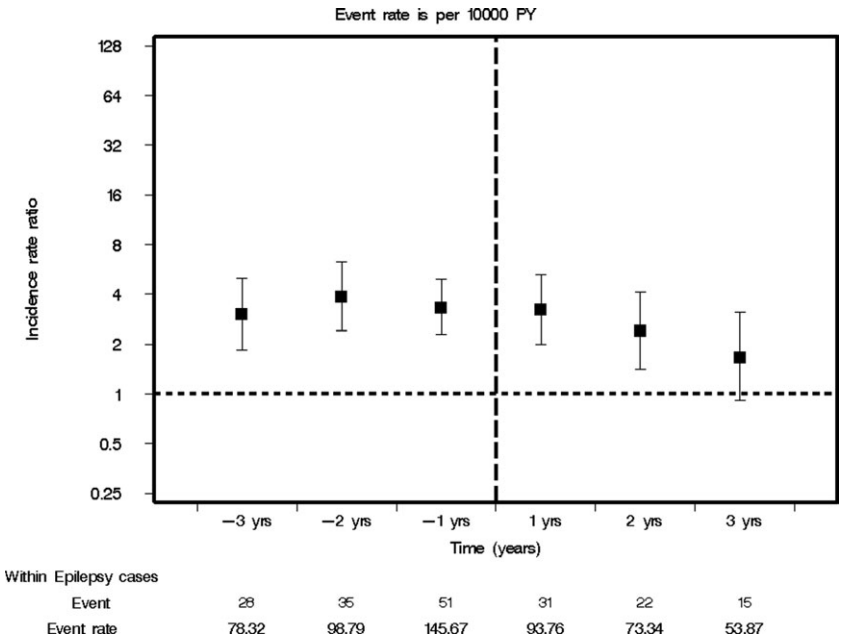

FIGURE 3: Trends in the incidence rate ratio for epilepsy versus controls with 95% confidence intervals for substance abuse and dependence in the 3 years before and 3 years after epilepsy diagnosis. PY = person-years.

diagnosis of epilepsy, history of depression is associated with a worse prognosis of epilepsy,[7] and lifetime history of psychiatric disorders is associated with a poor seizure prognosis after epilepsy surgery.[22] It is possible that some of the anxiety, depression, and suicidality that follows epilepsy may be due to the burden of having epilepsy or to side effects of antiepileptic drugs. More recent findings also support the presence of an underlying susceptibility to seizures and to selected psychiatric disorders whereby the psychiatric disorder is a marker of a decreased seizure threshold,[4] and in some people, seizures are a marker of increased susceptibility to develop psychiatric disorders.[19] Future studies of new onset psychiatric disorders following a diagnosis of epilepsy should evaluate each of these possibilities.

Our study is the first to demonstrate a 2-way relation between a broad spectrum of psychiatric disorders (ie, depression, anxiety, psychosis) and epilepsy. We found that first occurrences of these psychiatric disorders

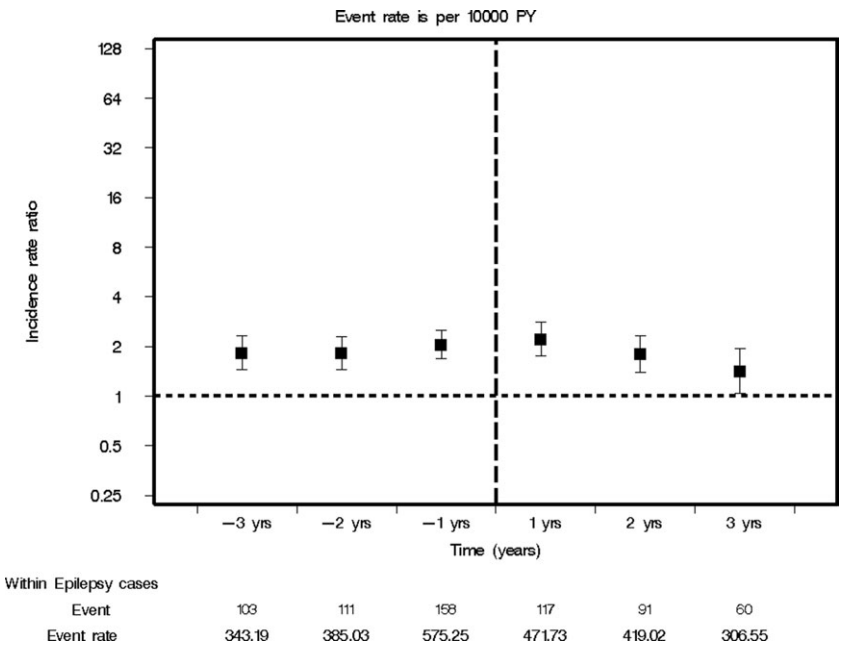

FIGURE 4: Trends in the incidence rate ratio for epilepsy versus controls with 95% confidence intervals for anxiety in the 3 years before and 3 years after epilepsy diagnosis. PY = person-years.

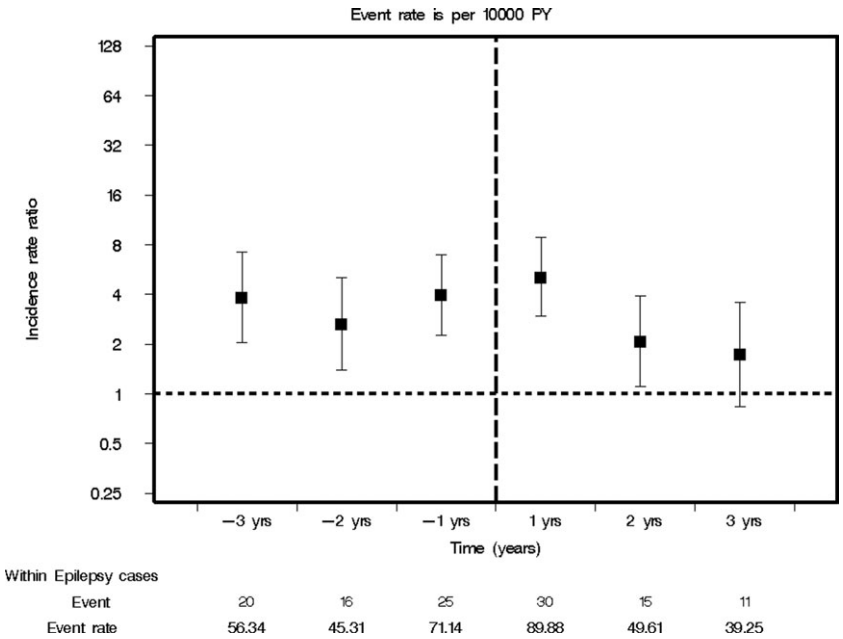

FIGURE 5: Trends in the incidence rate ratio for epilepsy versus controls with 95% confidence intervals for suicidality in the 3 years before and 3 years after epilepsy diagnosis. PY = person-years.

were significantly increased both before and after epilepsy diagnosis. Thus, the psychiatric disorders are both associated with increased risk for developing epilepsy, and following a diagnosis of epilepsy, the risk for developing the psychiatric disorders is increased. These associations persisted after excluding secondary causes of epilepsy and substance abuse and dependence. Relations were specific to the selected psychiatric disorders, as similar findings were only seen for acute surgery in the third year after epilepsy onset and for eczema only in the first year after epilepsy onset; the latter may be due to rashes in association with starting treatment with AEDs.

The long-held explanation for the increased risk for completed suicide in people with diagnosed epilepsy was that their epilepsy makes them severely depressed or anxious, leading to suicidal behavior. This may be 1 explanation, but recent findings suggest that this is unlikely to be the only explanation. In an Icelandic study,[4] suicide

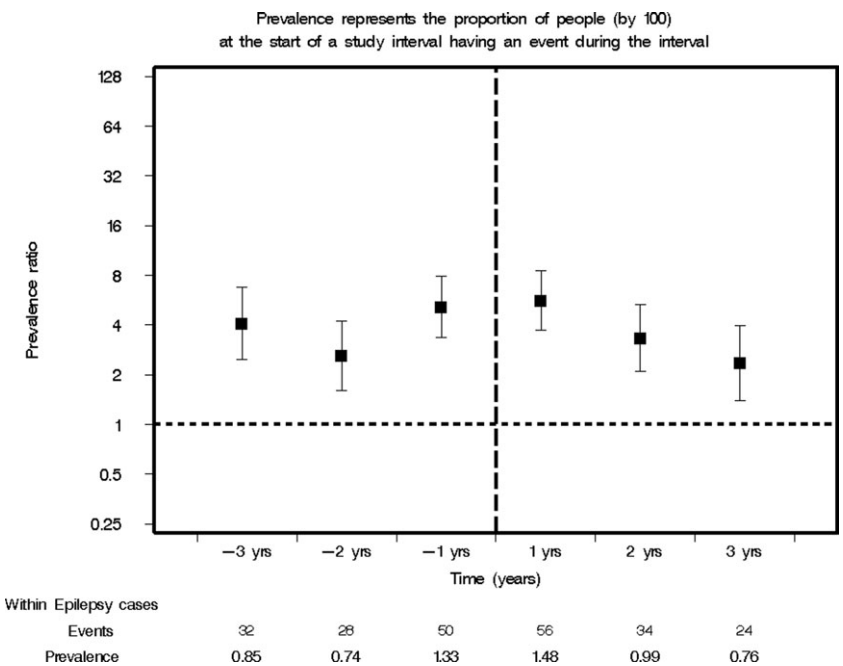

FIGURE 6: Trends in the prevalence ratio for epilepsy versus controls with 95% confidence intervals for suicidality in the 3 years before and 3 years after epilepsy diagnosis.

attempt was associated with a 3.5-fold increased risk for developing epilepsy (95% CI, 1.5–8.6), after adjusting for major depression, bipolar disorder, and cumulative alcohol intake. Because others have shown that suicide attempt increases the risk of later completed suicide,[23,24] the increased risk for completed suicide in people with epilepsy may also reflect recurrence of premorbid suicidal behavior in addition to possible consequences of the burden of having epilepsy and to potential side effects of antiepileptic drugs. We found a bidirectional relation between epilepsy and suicidality, with a significantly increased risk in all 3 years before epilepsy onset and in the 2 years after epilepsy onset. We also found an increased PR for suicidality in each of the 3 years before and after epilepsy onset, with recurrences predominating after epilepsy onset. The absence of a significant change in the association after diagnosis suggests there is no major effect of AEDs on suicide.[25,26] This is important because to date, studies have been limited to the period after epilepsy diagnosis, and associations found may be attributable to the disease rather than the treatment.

Although depression and anxiety are associated with many different neurological disorders, the association between epilepsy and psychosis appears to be unique. Recent studies have posited common underlying genetic etiology of psychosis and epilepsy, including copy number variants,[27] a subtype of calcium ion channel,[28] and a nicotinic acetylcholine receptor.[29] Common underlying etiology of epilepsy and psychosis is supported by our findings and new findings that the proportion with focal seizures, distribution of psychosis subtypes, and duration of psychotic episodes did not differ in a study comparing psychosis preceding and following epilepsy onset.[30] Recent results in a different population confirm our findings.[31]

Strengths and Weaknesses

Our study has several strengths, including the completeness of recordings in the GPRD database[9] and the population-based nature of the cohort, which is representative of the larger UK population.[10]

We were able to assemble a large enough study cohort to address a variety of psychiatric disorders, some with a low incidence in the general population. Several validation studies of psychiatric diagnoses have been performed in the GPRD[32,33] or in a subsample.[26] Findings include a positive predictive value of 91% for nonorganic psychosis,[32] 97% for suicide attempt, and 87% for completed suicide.[26] In a meta-analysis, the median proportion of cases confirmed for mental and behavioral disorders across 20 GPRD studies was 83%.[33]

We defined incident epilepsy according to the recording of a diagnosis of epilepsy and at least 2 AED prescriptions close in time to the recording of the epilepsy code, an approach that, although not formally validated,[34] has yielded an incidence of 50/100,000,[35] consistent with other population-based studies.[36] This comparison of rates is a form of external validation, and suggests that under- and overascertainment of epilepsy is unlikely in this study. Although misdiagnosis of epilepsy is a potential problem,[37] studies evaluating misdiagnosis have not included a requirement of at least 2 AED prescriptions as we have done. In validation of other neurological disorders in the GPRD, positive predictive values have been 92.7% for cerebrovascular disease and >83.2% for Alzheimer's disease[38]; the median proportion of cases confirmed was 81% in 25 validation studies of various neurological disorders.[33]

Controls were required to have a medical contact or prescription in the database, thus excluding people with no contact or prescription. This is a conservative approach that may limit generalizability and has the effect of biasing results toward the null.

Weaknesses include the use of diagnoses rather than administration of standardized interviews to make a diagnosis according to Diagnostic and Statistical Manual of Mental Disorders IV and suicidality diagnosis uniformly across cohort members. However, we do not think that the diagnoses were biased by the presence of epilepsy in this study, because the incidence of psychiatric disorders and suicidality was increased even before epilepsy onset compared to controls. Thus, this weakness has the effect of biasing our findings toward the null.

Conclusions

Epilepsy is associated with an increased onset of selected psychiatric disorders, both before and after epilepsy diagnosis. Additionally, there is a 2-way relation between epilepsy and suicidality. These relations suggest common underlying pathophysiological mechanisms that both lower seizure threshold and increase risk for psychiatric disorders and suicidality.

Acknowledgments

GlaxoSmithKline funded the purchase of the General Practice Research Database and the salaries of the GlaxoSmithKline employees involved in this paper.

We thank Drs K. Beach and C. Truong for their assistance with the coding of comorbidities in the GPRD database, M. Irizarry for his assistance in compiling a list of antiepileptic drugs, and Dr N. Galwey for his statistical support.

Authorship

D.C.H. had full access to all data and final responsibility for the decision to submit the manuscript for publication.

Potential Conflicts of Interest

L.I., L.M., D.J.W., and J.W. were employees of GlaxoSmithKline and L.I., D.J.W., and J.W. were stock option holders of GlaxoSmithKline at the time the work was conducted. D.C.H.: consulting, Pfizer, Mount Sinai Medical Center–Injury Prevention Center; travel support, GlaxoSmithKline; employment, Columbia University; grants/grants pending, CDC, NIH, AUCD, Epilepsy Foundation of America, Epilepsy Study Consortium. W.A.H.: travel support, GlaxoSmithKline; consultancy, Hotchkiss Brain Institute; employment, Columbia University; expert testimony, US Federal Air Administration.

References

1. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, Office of Translational Sciences, Office of Biostatistics. Statistical review and evaluations: Antiepileptic drugs and suicidality. Available online at http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM192556.pdf. Accessed on April 25, 2012.
2. Hesdorffer DC, Kanner AM. The FDA alert on suicidality and antiepileptic drugs: fire or false alarm? Epilepsia 2009;50:978–986.
3. Forsgren L, Bucht G, Eriksson S, Bergmark L. Incidence and clinical characterization of unprovoked seizures in adults: a prospective population-based study. Epilepsia 1996;37:224–229.
4. Hesdorffer DC, Hauser WA, Olafsson E, et al. Depression and suicide attempt as risk factors for incident unprovoked seizures. Ann Neurol 2005;59:35–41.
5. Nilsson FM, Kessing LV, Bolwig TG. On the increased risk of developing late-onset epilepsy for patients with major affective disorder. J Affect Disord 2003;76:39–48.
6. Forsgren L, Nystrom L. An incident case-referent study of epileptic seizures in adults. Epilepsy Res 1990;6:66–81.
7. Hitiris N, Mohanraj R, Norrie J, et al. Predictors of pharmacoresistant epilepsy. Epilepsy Res 2007;75:192–196.
8. Kanner AM, Byrne R, Chicharro A, et al. A lifetime psychiatric history predicts a worse seizure outcome following temporal lobectomy. Neurology 2009;72:793–799.
9. Jick H, Jick SS, Derby LE. Validation of information recorded on general practitioner based computerised data resource in the United Kingdom. BMJ 1991;302:766–768.
10. Jick SS, Kaye JA, Vasilakis-Scaramozza C, et al. Validity of the general practice research database. Pharmacotherapy 2003;23:686–689.
11. Kessler RC, Zhao S, Katz SJ, et al. Past-year use of outpatient services for psychiatric problems in the National Comorbidity Survey. Am J Psychiatry 1999;156:115–123.
12. Breslow NE, Day NE. Statistical methods in cancer research. Volume II: The design and analysis of cohort studies. Lyon, France: International Agency for Research on Cancer, 1987.
13. Beghi E, Spagnoli P, Airoldi L, et al. Emotional and affective disturbances in patients with epilepsy. Epilepsy Behav 2002;3:255–261.
14. Boylan LS, Flint LA, Labovitz DL, et al. Depression but not seizure frequency predicts quality of life in treatment-resistant epilepsy. Neurology 2004;62:258–261.
15. Tellez-Zenteno JF, Patten SB, Jette N, et al. Psychiatric comorbidity in epilepsy: a population-based analysis. Epilepsia 2007;48:2336–2344.
16. Baker GA, Jacoby A, Chadwick DW. The associations of psychopathology in epilepsy: a community study. Epilepsy Res 1996;25:29–39.
17. Hermann BP, Whitman S, Wyler AR, et al. Psychosocial predictors of psychopathology in epilepsy. Br J Psychiatry 1990;156:98–105.
18. Hesdorffer DC, Ludvigsson P, Olafsson E, et al. ADHD as a risk factor for incident unprovoked seizures and epilepsy in children. Arch Gen Psychiatry 2004;61:731–736.
19. Qin P, Xu H, Laursen TM, et al. Risk for schizophrenia and schizophrenia-like psychosis among patients with epilepsy: population based cohort study. BMJ 2005;331:23.
20. Vestergaard M, Pedersen CB, Christensen J, et al. Febrile seizures and risk of schizophrenia. Schizophr Res 2005;73:343–349.
21. Hesdorffer DC, Hauser WA, Annegers JF, Cascino G. Major depression is a risk factor for seizures in older adults. Ann Neurol 2000;47:246–249.
22. Kanner AM. Does a history of postictal psychosis predict a poor postsurgical seizure outcome? Epilepsy Curr 2009;9:96–97.
23. Bradvik L. Suicide after suicide attempt in severe depression: a long-term follow-up. Suicide Life Threat Behav 2003;33:381–388.
24. Suominen K, Isometsa E, Suokas J, et al. Completed suicide after a suicide attempt: a 37-year follow-up study. Am J Psychiatry 2004;161:562–563.
25. Patorno E, Bohn RL, Wahl PM, et al. Anticonvulsant medications and the risk of suicide, attempted suicide, or violent death. JAMA 2010;303:1401–1409.
26. Arana A, Wentworth CE, Ayuso-Mateos JL, Arellano FM. Suicide-related events in patients treated with antiepileptic drugs. N Engl J Med 2010;363:542–551.
27. Friedman JI, Vrijenhoek T, Markx S, et al. CNTNAP2 gene dosage variation is associated with schizophrenia and epilepsy. Mol Psychiatry 2008;13:261–266.
28. Green EK, Grozeva D, Jones I, et al. The bipolar disorder risk allele at CACNA1C also confers risk of recurrent major depression and of schizophrenia. Mol Psychiatry 2010;15:1016–1022.
29. Magnusson A, Stordal E, Brodtkorb E, Steinlein O. Schizophrenia, psychotic illness and other psychiatric symptoms in families with autosomal dominant nocturnal frontal lobe epilepsy caused by different mutations. Psychiatr Genet 2003;13:91–95.
30. Adachi N, Onuma T, Kato M, et al. Analogy between psychosis antedating epilepsy and epilepsy antedating psychosis. Epilepsia 2011;52:1239–1244.
31. Chang YT, Chen PC, Tsai IJ, et al. Bidirectional relation between schizophrenia and epilepsy: a population-based retrospective cohort study. Epilepsia 2011;52:2036–2042.
32. Nazareth I, King M, Haines A, et al. Accuracy of diagnosis of psychosis on general practice computer system. BMJ 1993;307:32–34.
33. Herrett E, Thomas SL, Schoonen WM, et al. Validation and validity of diagnoses in the General Practice Research Database: a systematic review. Br J Clin Pharmacol 2010;69:4–14.
34. Holden EW, Grossman E, Nguyen HT, et al. Developing a computer algorithm to identify epilepsy cases in managed care organizations. Dis Manag 2005;8:1–14.
35. Martinez C, Sullivan T, Hauser WA. Prevalence of acute repetitive seizures (ARS) in the United Kingdom. Epilepsy Res 2009;87:137–143.
36. Banerjee PN, Filippi D, Allen Hauser W. The descriptive epidemiology of epilepsy: a review. Epilepsy Res 2009;85:31–45.
37. Chowdhury FA, Nashef L, Elwes RD. Misdiagnosis in epilepsy: a review and recognition of diagnostic uncertainty. Eur J Neurol 2008;15:1034–1042.
38. Khan NF, Harrison SE, Rose PW. Validity of diagnostic coding within the General Practice Research Database: a systematic review. Br J Gen Pract 2010;60:e128–e136.