Original Investigation

Occurrence and Recurrence of Attempted Suicide Among People With Epilepsy

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IMPORTANCE People with epilepsy have a 5-fold increased risk of suicide. Less is known about attempted suicide and whether psychiatric disorders and antiepileptic drugs modify the risk of attempted suicide.

OBJECTIVES To estimate the magnitude of the association between attempted suicide and epilepsy by comparing a first suicide attempt and a second suicide attempt (hereafter referred to as a recurrent suicide attempt) among people before they received a diagnosis of epilepsy (case patients) with a first suicide attempt and a recurrent suicide attempt among people without epilepsy (control patients), and to evaluate the effect of comorbid psychiatric disorders and the exclusion of antiepileptic drug prescriptions on this association.

DESIGN, SETTING, AND PARTICIPANTS Population-based retrospective cohort study in the United Kingdom of case patients with incident epilepsy and control patients without a history of epilepsy in a general practice setting using Clinical Practice Research Datalink. The case patients with incident epilepsy were identified between 1987 and 2013 and were 10 to 60 years of age. The control patients for each case patient were 4 randomly selected people who did not receive a diagnosis of epilepsy before the case patient’s epilepsy was diagnosed (the index date), matched by year of birth, sex, and general practice for a control to case ratio of 4 to 1.

MAIN OUTCOMES AND MEASURES Hazard ratio for incident and recurrent suicide attempts among case patients with epilepsy compared with control patients without.

RESULTS For 14,059 case patients (median age, 36 years [range, 10-60 years]) who later had an onset of epilepsy vs 56,184 control patients (median age, 36 years [range, 10-60 years]), the risk was increased 2.9-fold (95% CI, 2.5- to 3.4-fold) for a first suicide attempt during the time period before the case patients received a diagnosis of epilepsy. For 278 case patients (median age, 37 years [range, 10-61 years]) who later had an onset of epilepsy vs 434 control patients (median age, 35 years [range, 11-61 years]), the risk was increased 1.8-fold (95% CI, 1.3- to 2.5-fold) for a recurrent suicide attempt up to and including the day that epilepsy was diagnosed. Exclusion of antiepileptic drugs prescribed before the index date did not meaningfully alter the findings, nor did separate analyses of patients with and patients without diagnosed psychiatric disorders.

CONCLUSIONS AND RELEVANCE Suicide attempts and recurrent suicide attempts are associated with epilepsy even before epilepsy manifests, suggesting a common underlying biology. Our findings indicate that both incident and recurrent suicide attempts are associated with incident epilepsy in the absence of antiepileptic drugs and in the absence of diagnosed psychiatric disorders, further strengthening the evidence for a common underlying etiology with an as-yet-unknown mechanism.

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O ccurrences of suicide, attempted suicide, and suicidal ideation are increased among people with prevalent epilepsy compared with controls. Based on these associations, clinicians have concluded that epilepsy increases the risk for suicidal thoughts and behavior. However, in a meta-analysis of clinical trial data, the US Food and Drug Administration (FDA) concluded that antiepileptic drugs (AEDs) increase the risk for suicidal thoughts and behaviors in people with epilepsy, psychiatric disorders, or other disorders and mandated a warning label for all AEDs. In the meta-analysis, no information was included on patients’ prior suicidal thoughts or behaviors or psychiatric history. The FDA nevertheless concluded that AEDs, randomized as adjunctive therapy vs placebo for people with epilepsy, were associated with an increased risk for suicidal thoughts and behaviors in people with epilepsy.

Following the FDA publication, observational studies considered the possible relationship between different AEDs and suicidal thoughts and behaviors in people with epilepsy. Unfortunately, different AED referents were used, and confounding by indication was possible. Two studies took a different approach. One study compared the number of suicide attempts among AED-treated people with epilepsy with the number of suicide attempts among a control group of people who were not treated with AEDs and found no association. Another study found that suicidal thoughts may prompt the prescription of an AED.

The relationship between epilepsy and attempted suicide may reach beyond a possible effect of AEDs. Several studies have shown that an attempted suicide is associated with an increased risk for developing epilepsy. The relationship is bidirectional because incident epilepsy is also associated with an increased risk for a first-ever suicide attempt. We have previously suggested that the association between attempted suicide and incident epilepsy may be due to a common underlying etiology, but other explanations are possible.

For example, one further possibility is that psychiatric disorders, which are known to be associated with epilepsy, may mediate the association of attempted suicide with epilepsy before the onset of epilepsy. Other studies have shown that psychiatric disorders are associated with an increased risk for completed suicide among people with epilepsy compared with controls. However, one study found an increased risk for suicide among people with epilepsy in the absence of psychiatric disorders, arguing against the idea that psychiatric disorders mediate the association. It is also possible that, in these studies, AEDs, which are used to treat epilepsy and/or psychiatric disorders, may mediate the association of epilepsy with suicidal thoughts and behaviors. We performed an analysis using the UK Clinical Practice Research Datalink (CPRD) and comparing the risk for attempted suicide among people who eventually developed incident epilepsy with that among controls. We hypothesized that (1) the risk of attempted suicide is increased before the first appearance of epilepsy, (2) the association between attempted suicide and epilepsy is observed among those persons not prescribed AEDs, and (3) the association between epilepsy and attempted suicide is observed among those persons with and without psychiatric diagnoses.

Methods
The CPRD contains detailed information on diagnoses, prescriptions, investigations, risk factors, outcomes, and hospital referrals, together with basic demographic information for a sample of approximately 13 million people throughout the United Kingdom from 1987 through 2013. Approximately 5.5 million people were actively followed up in the database at the time of analysis. The data are obtained from the computer systems used by general practitioners to maintain the clinical records within their practices. The UK Medicines and Healthcare Regulatory Agency monitors data quality; practices that fail to maintain the required standards are removed. The completeness and accuracy of the clinical records have been validated externally. The database is a population-based database and is representative of the age, sex, and geographic regions of the United Kingdom; hence, the results are broadly applicable to the wider UK population.

Study Population
Our general methods have been described elsewhere. In brief, in our new study, the CPRD database was used to identify cases of newly diagnosed (incident) epilepsy and matched controls without a history of epilepsy. Our study uses all of the available patient history, which includes information prior to enrollment in the CPRD until December 29, 2013. We obtained approval for our study from the Independent Scientific Advisory Committee for Medicines and Healthcare products Regulatory Agency Database Research. Informed consent was not obtained from patients because the data were deidentified.

Case Patients
The case patients were 10 to 60 years of age with incident epilepsy and were included in our study if they had at least 1 epilepsy CPRD medical Read code recorded between 1988 and 2013. Also, at least 2 AED prescriptions had to be listed from the month before to 6 months after the index date to confirm the epilepsy diagnosis at the index date. This method has been validated in The Health Improvement Network, a 5% sample of the CPRD.

Control Patients
Four control patients without a diagnosis of epilepsy any time before the case patient’s index date were randomly selected and matched to each case by year of birth, sex, and general practice. Consistent with incidence density sampling, qualifying control patients were included who later developed epilepsy 1 year or more after their control index date. Case patients and control patients were required to have at least 6 months of full clinical records prior to the index date and at least 1 day of history afterward. In addition, they had 1 or more CPRD medical (eg, annual physical examination and heart disease) or drug codes for a condition other than epi-
lepsy in the 6 months before the index date to ensure that they were actively seeking care around the index date.

**Outcomes**

Clinical data are currently recorded in primary care using Clinical Terms version 3 terminology (Read codes). Historical data recorded as Oxford Medical Information Systems codes, based on the ICD and Office of Population and Census Statistics operation codes, have also been translated into equivalent Read codes on the CPRD. The CPRD medical codes were used to identify attempted suicides up to and including the index date. Whenever diagnoses of interest were present before the study period, even before CPRD entry, diagnoses during the study period were considered recurrent.

**Covariates**

The CPRD codes were used to identify the psychiatric disorders previously found to be associated with epilepsy, including major depression, anxiety, and psychosis (schizophrenia, mania, reactive psychosis, and other nonorganic psychoses), bipolar disorder, and substance abuse and dependence with regard to alcohol and drugs before CPRD entry and during CPRD participation. In several validation studies of psychiatric diagnoses in the CPRD, the positive predictive value of CPRD codes, relative to the true diagnosis, was 91% for non-organic psychosis, 97% for suicide attempt, and 87% for completed suicide. In a meta-analysis, the median proportion of cases confirmed for mental and behavioral disorders across 20 CPRD studies was 83%.

**Statistical Analysis**

Data were analyzed using SAS version 9.3 (SAS Institute Inc.). Cox proportional hazards regression was used, and the hazard ratio (HR) and 95% CI for the association of suicide attempt with case status were calculated. An α level of less than .05 was considered statistically significant, and 2-sided tests were used for all analyses.

With regard to the increased risk for a first suicide attempt or a recurrent suicide attempt (hereafter referred to as a recurrent suicide attempt) prior to the first appearance of epilepsy, we performed a crude analysis to compare case patients with control patients, adjusting for the matching variables, and we performed further adjusted analyses to account for age and sex and specified a history of psychiatric disorder as a time-varying covariate. There was no statistically significant evidence of an interaction between psychiatric disorders and case status, and no interaction term was included in the model.

With regard to the increased risk for a first suicide attempt or a recurrent suicide attempt, we used 2 separate Cox models, one of patients without psychiatric disorders and the other of patients with psychiatric disorders, to estimate the association between (1) a first suicide attempt and (2) a recurrent suicide attempt among case patients compared with control patients prior to the first appearance of epilepsy, with adjustment for age and sex. Some case patients and control patients contributed to both models if those patients originally without psychiatric disorders eventually received a diagnosis of a psychiatric disorder. In this case, person-time was allocated to each of these conditions.

With regard to the increased risk for a first suicide attempt or a recurrent suicide attempt prior to the first appearance of epilepsy in those patients not prescribed AEDs, we performed further Cox analyses, excluding case and control patients prescribed AEDs before the index date. Additional analyses excluded case and control patients with secondary causes of epilepsy.

**Results**

For both the 14 059 case patients with incident epilepsy and the 56 184 control patients without epilepsy, the median age was 36 years (Table 1), and 51.8% of patients were male in both groups. Idiopathic/cryptogenic epilepsy was present in 85.3% of case patients. Psychiatric disorders were diagnosed on or before the index date for 32.5% of case patients and 22.5% of control patients (P < .001).

There were 278 case patients and 434 control patients who had a first suicide attempt during the time up to and includ-
ing the index date. The median age was 37 years for case patients and 35 years for control patients. Male patients accounted for 52.9% of the case patients and 50.7% of the control patients, and 86.3% of these male patients had idiopathic/cryptogenic epilepsy. The ratio of male to female patients was 1.12 for case patients and 1.03 for control patients. The ratio remained close to 1:1 for case and control patients when prior AED use and/or secondary causes of epilepsy were excluded.

Among the 14,059 case patients with incident epilepsy and 56,184 control patients without epilepsy, the risk for a first suicide attempt during the time up to and including the index date was 2.4-fold (95% CI, 2.0- to 2.9-fold) greater for case patients than control patients, adjusting for age, sex, and psychiatric disorders as a time-varying covariate. The results were similar when patients with AED prescriptions were excluded from analyses of first suicide attempts (Table 2).

The risk for a first suicide attempt up to and including the onset of epilepsy was increased 2.5-fold (95% CI, 1.9- to 3.2-fold) for case patients with psychiatric disorders compared with control patients with psychiatric disorders, after adjusting for age and sex. The risk was increased 2.6-fold (95% CI, 2.2- to 3.2-fold) for case patients compared with control patients in the absence of psychiatric disorders. After excluding both case and control patients who were prescribed AEDs, we found that the risk for a first suicide attempt was increased 2.3-fold (95% CI, 1.8- to 3.0-fold) for case patients with psychiatric disorders compared with control patients with psychiatric disorders and was increased 2.3-fold (95% CI, 1.7- to 3.2-fold) for case patients without psychiatric disorders compared with control patients without psychiatric disorders (Table 3).

Among the 278 case patients who attempted suicide for the first time and then later developed epilepsy and the 434 control patients without epilepsy, the risk for a recurrent suicide attempt during the time up to and including the index date was 1.8-fold (95% CI, 1.3- to 2.5-fold) greater for case patients than control patients, after adjusting for age, sex, and psychiatric disorders as a time-varying covariate. After excluding both case and control patients who were prescribed AEDs, we found that the risk for a recurrent suicide attempt was unchanged (Table 2).

After adjusting for age and sex, we found that the risk for a recurrent suicide attempt was statistically significantly increased for case patients with epilepsy compared with control patients in the presence and in the absence of psychiatric disorders (HR, 1.6 [95% CI, 1.1-2.4]; HR, 2.7 [95% CI, 1.4-5.3]). After excluding case and control patients who were prescribed AEDs in adjusted analysis, we found that the HR was not statistically significantly increased in the presence of diagnosed psychiatric disorders but was statistically significantly increased in the absence of diagnosed psychiatric disorders (HR, 2.5 [95% CI, 1.01-6.1]) (Table 3). The results of all analyses were unchanged when they were repeated after ex-
Including secondary causes of epilepsy, which are themselves associated with psychiatric disorders and suicide in some instances (eTables 1 and 2 in the Supplement).

Discussion

To our knowledge, the present study is the first to report the associations between incident epilepsy and incident and recurrent suicide attempts and to describe the associations among people with or without diagnosed psychiatric disorders. We found that, during the time before onset of epilepsy, the risk was increased for a first suicide attempt and for a recurrent suicide attempt among patients who later developed epilepsy compared with control patients. Moreover, we found that the strength of association with attempted suicide was similar for those with and those without diagnosed psychiatric disorders. Thus, our findings are consistent with the hypothesis of a common underlying susceptibility to both attempting suicide and epilepsy that is not mediated by psychiatric disorders. This is similar to a study showing that, although depression was associated with an increased risk for developing epilepsy, in analyses that adjusted for all other symptoms, the only specific factor that was associated with epilepsy was attempted suicide.

In models adjusted for age, sex, and diagnosed psychiatric disorders as a time-varying covariate, we found that the HR for suicide attempt and recurrent suicide attempt was increased for those patients who later developed epilepsy compared with control patients. The findings were similar in analyses that included the entire sample, in analyses that excluded those patients who were prescribed AEDs, and in analyses that excluded secondary causes of epilepsy. A weakness of the analysis that included AEDs is that our study is an observational study and not a clinical trial, and there is potential for confounding by indication. Therefore, we draw no inferences about the effects of AEDs. However, in the analysis that excluded AEDs, we suggest that there is a common susceptibility to both attempting suicide and epilepsy.

In epidemiological population-based studies of incident epilepsy, male patients predominate. In our study, 51.8% of the case patients with epilepsy were male patients. If suicide attempt is associated with an increased risk of epilepsy, the proportion of male patients who attempted suicide would be higher for case patients with epilepsy than for control patients. This is weakly reflected in our study; the ratio of male to female patients among those who attempted suicide was 1.12 for case patients and 1.03 for control patients.

Epilepsy and attempted suicide have common features, in both epidemiology and neurobiology. Attempted suicides and epileptic seizures are episodic phenomena that share similar recurrence risks and risk factors. In a Danish population-based study of first suicide attempts, the risk for a recurrent suicide attempt was 37.3% after 5 years, with most recurring in the first 2 years. This parallels the 32% risk of a recurrent seizure after incident unprovoked seizure over 5 years, with most seizures recurring in the first 2 years. Attempted suicide and epilepsy share psychiatric risk factors, including depression, anxiety, attention-deficit/hyperactivity disorder, alcohol abuse or dependence, and psychosis. Other episodic disorders, including migraine with aura and multiple sclerosis, are also risk factors for developing epilepsy and for attempted suicide. In addition, low socioeconomic status is a risk factor for both disorders. Neurobiological reviews of attempted suicides suggest that neurotransmitters and their receptors (eg, serotonin, glutamate, and γ-aminobutyric acid), lipids, stress systems, astrocytes, and oligodendrocytes may all contribute, and all are implicated in epilepsy.

The FDA meta-analysis implicated AEDs as the cause of suicidal thoughts and behaviors and mandated a warning label in all drug inserts. Observational studies of AEDs and suicidal thoughts and behaviors followed the FDA report. These were methodologically limited and showed a lack of concordance owing, in part, to differences in the referent AED. In addition, these analyses ignored the possibility that incident and recurrent suicide attempts may have preceded AED use. Our study addresses this by considering the occurrence and recurrence of suicide attempts prior to the onset of epilepsy.

A limitation of our study, not previously discussed, is that we are unable to distinguish the seizures of epilepsy from dissociative nonepileptic seizures in the CPRD. However, an Icelandic study found that the incidence of nonepileptic seizures was 3 in 100 000 person-years of observation, whereas the incidence of epilepsy ranged from 50 to 60 in 100 000 person-years of observation. Thus, the presence of nonepileptic seizures is unlikely to have a meaningful effect on our results.

The FDA warning label for all AEDs covers all indications and mandates physicians to ask their patients about suicidal thoughts and behaviors. Following the FDA warning, a survey of epilepsy specialists in academic settings found that 62% did not use a scale to screen for depression and that 46% did not think that the FDA warning would alter their practice. In discussions with patients, 98% of these specialists discussed the behavioral effects at initiation of AEDs, but only 44% discussed suicidal thoughts and behaviors, which perhaps indicates a level of discomfort regarding these issues.

Conclusions

Among the risk factors for completed suicide, prior suicide attempts by any method is the strongest, conferring a 38.4-fold increased risk compared with the general population. Eight different psychiatric disorders follow in the review by Harris and Barraclough with a 8.5- to 20.4-fold increased suicide risk. Epilepsy has the 10th greatest risk for completed suicide, increasing the risk 5-fold, greater than anxiety and alcohol dependence. Thus, physicians treating patients with epi-
suicide and the treatment of psychiatric disorders for people with epilepsy. The prevention of suicide and the treatment of psychiatric disorders for people with epilepsy falls short of that offered to the larger population of people with psychiatric diagnoses and/or suicidal thoughts and behaviors. The creation of partnerships between neurologists, epilepsy specialists, psychiatrists, and other mental health professionals are needed to improve the diagnosis and treatment of psychiatric disorders in people with epilepsy. Such partnerships may allow for the development of suicide prevention programs for people with epilepsy, with and without psychiatric disorders, to prevent the loss of life and improve the quality of life.

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Study concept and design: Hesdorffer, Ishihara, Mynepalli, Hauser.

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Study supervision: Webb.

Conflict of Interest Disclosures: Drs Ishihara and Galwey, Mr Webb, and Ms Mynepalli are paid employees of GSK. Dr Hesdorffer is on advisory boards for Upsher-Smith and Acorda and is a consultant to Cyberonics. She is a consultant to the NYU Langone Medical Center’s Epilepsy Division and to Mount Sinai’s Injury Prevention Center in the Department of Rehabilitation Medicine. She serves as associate editor for Epilepsy and is on the editorial boards of Epilepsy and Behavior and Epilepsy Research. She is a contributing editor for Epilepsy Currents. She receives grant funding from the National Institutes of Health, the Centers for Disease Control and Prevention, the Patient-Centered Outcomes Research Institute, the Epilepsy Foundation, and the Epilepsy Study Consortium. Mr Webb, Ms Mynepalli, and Dr Galwey are shareholders of GSK. Dr Ishihara was an employee of GSK while working on this study and is a shareholder of GSK but has moved to Lundbeck SAS. Dr Hauser was a consultant to the Federal Aviation Administration, has received funding for travel from the American Epilepsy Society, and has received research support from the Centers for Disease Control and Prevention. He is on the editorial advisory boards of Epilepsy Research, Acta Neurologica Scandinavica, and Neuroepidemiology. He is a member of a safety monitoring board for NeuroPace.

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