EPILEPSY CURRENTS

Current Literature
In Clinical Science

Epilepsy and Suicidality: What's the Relationship?

Occurrence and Recurrence of Attempted Suicide Among People With Epilepsy.

Hesdorffer DC, Ishihara L, Webb DJ, Mynepalli M, Galwey NW, Hauser WA. *JAMA Psychiatry* 2016;73:80–86.

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.

Commentary

Suicidal thoughts and behaviors are known to be increased among persons with epilepsy (1). Reasons for this association remain unclear, and different explanations have been proposed. One school of thought is that epilepsy itself increases the risk; this view is supported by studies finding that incident epilepsy is associated with an increased risk for a first-ever suicide attempt (2, 3). A meta-analysis of clinical trial data of 11 antiepileptic drugs (AEDs), however, led the FDA to conclude that AEDs are associated with an increased risk of suicidality relative to placebo in randomized placebo-controlled trials (4). These randomized controlled trials were not originally designed to investigate suicidality, and no information was provided about patients' prior suicidal thoughts or behaviors or psychiatric history. This relationship is not consistently found as seen in the results of an observational study comparing the incidence rate of suicide-related events among 1) patients without epilepsy, depression, bipolar disorder, or AED treatment; 2) patients with epilepsy who did not receive AED treatment; and 3) patients with epilepsy who received AEDs (5). Adjusted analyses found that AED therapy was not associated with an increased risk of suicide-related events among patients with epilepsy. Other studies reveal yet another possible relationship in that a history of attempted suicide was associated with an increased risk of developing epilepsy (2, 3, 6). An important confounding factor or mediator is comorbid psychiatric disorders. The epilepsy community is increasingly aware of the high percentages of psychiatric disorders among persons with epilepsy. Some studies find that psychiatric disorders are associated with an increased risk of suicide completion among persons with epilepsy compared with controls

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(7, 8), whereas one study found an increased risk for suicide in the absence of psychiatric disorders (9). These multiple associations, explanations, and potential confounders demonstrate the need for a well-designed and controlled study that will allow us to better understand the relationships among suicidality, epilepsy, AED therapy, and psychiatric disorders. Hesdorffer and colleagues have performed a timely, much-needed, population-based retrospective cohort study aimed at estimating the magnitude of the association between prior attempted suicide(s) and incident epilepsy and evaluating the effect of comorbid psychiatric disorders and the exclusion of AED prescriptions on this association.

Using the United Kingdom Clinical Practice Research Datalink, case patients with incident epilepsy (n = 14,059) and control patients (n = 56,184) without a history of epilepsy were identified. Case patients included patients aged 10 to 60 years with at least one epilepsy medical code and at least two AED prescriptions listed from the month before to six months after the index date. The index date refers to the date that a case patient was diagnosed with epilepsy. Four control patients without a diagnosis of epilepsy at 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. The main outcome measure was the hazard ratio for incident and recurrent suicide attempts among case patients who were later diagnosed with epilepsy compared with controls with no epilepsy diagnosis, allowing the investigators to compare suicide attempts, first time and recurrent, between case patients and controls prior to the diagnosis of epilepsy. Statistical analysis was performed using Cox proportional hazard regression. Studied covariates included diagnosis of psychiatric disorders as identified by medical codes for major depression, anxiety, psychosis (schizophrenia, mania, reactive psychosis, and nonorganic psychoses), bipolar disorder, substance abuse, and dependence with regard to alcohol and drugs. Analysis also looked at the effect of AED prescriptions prior to epilepsy diagnosis. These prescriptions included AED prescriptions for indications other than seizures or epilepsy. Of interest, approximately 40% of subjects in the case and control groups had previously been prescribed AEDs, which reflects the growing use of these drugs for indications other than seizures, particularly for psychiatric conditions. Psychiatric disorders were diagnosed on or before the index date for 32.5% of case patients and for 22.5% of control patients.

The risk for a first suicide attempt during the time up to and including the index date was higher for case patients than for control patients when the groups were compared without exclusions, after AED prescription exclusion, and when comparing case and controls with and without psychiatric disorders. After adjusting for age, sex, and psychiatric disorders, the risk for a first suicide attempt was 2.4-fold (95% confidence interval [CI]: 2.0- to 2.9-fold) higher among the case patients than control patients. The results were similar when patients with AED prescriptions were excluded. After adjusting for age and sex, the risk for a first suicide attempt was 2.5-fold higher (95% CI: 1.9- to 3.2-fold) for case patients with psychiatric disorders when compared with control patients with psychiatric disorders. Similarly, the risk was increased 2.6-fold (95% CI: 2.2- to 3.2-fold) for case patients when compared with control patients who did not have a diagnosis of psychiatric disorders. Results were again consistent when the authors compared those with and without psychiatric disorders in the absence of AED prescriptions. These results clarify that the risk of a first suicide attempt was higher in patients who were later diagnosed with epilepsy independent of diagnosed psychiatric conditions and AED prescriptions.

The risk for recurrent suicide during the time up to and including the index date was also greater for case patients than control patients. After adjusting for age, sex, and psychiatric disorders as a time-varying covariate, the risk for recurrent suicide attempt was 1.8-fold (1.3- to 2.5-fold) greater for case patients than controls. As with first-time suicide attempts, excluding those prescribed AEDs did not affect the results. After adjusting for age and sex and comparing those with and without psychiatric disorders separately, the risk was again increased for case patients when compared with controls (those with psychiatric disorders: 1.6-fold increased [95% CI: 1.1- to 2.4-fold]; those without psychiatric disorders: 2.7-fold increased [95% CI: 1.4- to 5.3-fold]). After excluding case patients and controls who were prescribed AEDs, the hazard ratio was not significantly increased in the presence of diagnosed psychiatric disorders but was significantly increased in the absence of psychiatric disorders.

Overall, statistical comparisons in this population-based retrospective study find a consistent increased risk of first-ever and recurrent suicide among case patients who developed incident epilepsy independent of prior AED prescriptions or psychiatric diagnoses. These results suggest that the biological or genetic makeup (or both) of persons who are diagnosed with epilepsy also puts them at risk for suicidality. If you step back and look at these conditions, there are common features. For example, they are both cyclical, with intermittent and acute presentations of symptoms. Future genetic and pathological studies should consider looking at incident epilepsy and suicidality together to better elucidate mechanisms, treatment, and prevention of these potentially devastating conditions.

Hesdorffer and colleagues have not only provided us with a well-designed and controlled study that clarifies the relationships among suicidality, epilepsy, AED therapy, and psychiatric disorders, but their results provide an example of the rigor needed when performing epidemiologic studies looking for potential associations. Much of the confusion about why patients with epilepsy are at higher risk for suicidality is because of poorly designed studies finding associations and risk factors that are not independently associated with suicidality in persons with epilepsy.

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