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SUICIDALITY AND EPILEPSY: A COMPLEX RELATIONSHIP THAT REMAINS MISUNDERSTOOD AND UNDERESTIMATED

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Suicidality in people with epilepsy is significantly more frequent than in the general population. The relation between suicidality and epilepsy is multifactorial and bidirectional. The purpose of this review is to highlight the most important psychiatric, pharmacologic, and epilepsy-related variables linked to the increased suicidal risk among these patients.

There is a general consensus that suicidality, which encompasses completed suicide, suicide attempt, and suicidal ideation, is significantly more frequent among people with epilepsy than in the general population (1–5). Yet, suicidality and its associated psychiatric disorders remain underrecognized and untreated. A recent alert from the FDA, suggesting that antiepileptic drugs (AEDs) increase suicide risk, has kindled significant interest in this issue (6). The relationship between epilepsy and suicidality is complex and multifactorial. Thus, the aim of this article is to review the most relevant psychiatric, pharmacologic, and epilepsy-related variables associated with increased suicidality risk for people with epilepsy and provide practical strategies to identify those risk factors.

Epidemiologic Data

Suicide attempts are found with relative frequency in epilepsy. A mean of 11.5% (range: 0–67%) of deaths of patients with chronic epilepsy were attributed to suicide in a review of 21 studies (2). A recent population-based Danish study found that individuals with epilepsy had a three-fold higher risk of suicide as a cause of death (relative risk [RR], 3.17; 95% confidence intervals [CI]: 2.88–3.5) than controls (1). In a cross-sectional study, Jones et al. found a 20.8% lifetime prevalence of suicide attempts among 139 outpatients followed in five tertiary epilepsy centers in the United States (2). A Canadian population-based study demonstrated a 25% lifetime prevalence of suicidal ideation for people with epilepsy compared with 12.2% of controls (7).

A history of suicide attempt is the strongest predictor of a future completed suicide. For example, Harris and Barraclough found that people with epilepsy who attempted suicide had a 38.4% increased risk for later completed suicide compared with the general population (5). Likewise, in a Swedish population-based study, a previous suicide attempt was identified in 46.2% of people with epilepsy who eventually committed suicide (4).

Bidirectional Relation between Epilepsy and Suicidality

Not only do people with epilepsy have a higher risk of suicide, but conversely, one population-based study identified a five-fold higher risk for developing epilepsy among individuals who exhibited suicidality prior to the onset of epilepsy (8). This risk was independent of a history of major depressive disorder and alcohol abuse. In addition, two other population-based studies found that people with a history of depression have a four- to seven-fold higher risk of developing epilepsy (9,10). Furthermore, the co-occurrence of migraine with aura (but not migraine without aura), major depression, and suicidality increase the risk of unprovoked seizures by more than six-fold (11); these data may be explained by abnormal brain serotonin activity (12).

Psychiatric Risks Factors

After controlling for comorbid socioeconomic status and psychiatric comorbidities, the Danish population-based study previously mentioned found that the patients with epilepsy had nearly twice the risk of committing suicide (RR, 1.99; 95% CI: 1.71–2.32) than controls (1). However, the risk increased almost 14-fold when comorbid psychiatric disorders were present, particularly with mood (32-fold) and anxiety (12-fold) disorders. Of note, the study found that the risk of suicide was greatest during the first 6 months after the diagnosis of epilepsy (RR, 5.4; 95% CI: 4.4–8.3) and was even higher in the presence of comorbid psychiatric disorders (RR, 29.2; 95% CI: 16.4–51.9) during this early period. Similarly, a Swedish

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study demonstrated that comorbid psychiatric disorders were associated with a nine-fold increase in the risk of suicide and a 10-fold increase for patients also using antipsychotic drugs (13). In the previously discussed Jones et al. study, the highest risks for a suicide attempt were correlated with a lifetime history of major depressive episode (odds ratios [OR], 5.9; 95% CI: 2.4–14.3) and lifetime manic episode (OR, 12.6; 95% CI: 1.3–125.9) (2). Likewise, a lifetime history of mood or anxiety disorders was identified as significantly associated with the risk of suicidal ideation.

Epilepsy-Related Risk Factors

Only one study investigated postictal suicidal ideation in a systematic manner (14). Among 100 consecutive patients, 13% experienced suicidal ideation at a median duration of 24 hours after more than 50% of their seizures. These patients were significantly more likely to have had a past history of bipolar or major depressive disorders as well as of psychiatric hospitalization. Suicidal behavior also has been reported in the context of postictal psychotic episodes. For instance, in a study of patients with temporal lobe epilepsy, Kanemoto et al. reported that suicide attempts were more frequent during postictal psychotic episodes (7%) than during either acute interictal psychosis (2%) or postictal confusion (0%) (15).

Type of Epilepsy Syndrome

An increased suicide risk of as much as 6- to 25-fold was reported to be associated with temporal lobe epilepsy (16–18; however, not all studies supported this finding (3,12). Furthermore, having undergone epilepsy surgery has been associated with higher suicide rates (24% of all deaths) compared with the rates in nonsurgical series, whether or not seizure-free state was achieved (19). Future studies with larger number of subjects are necessary to clarify these data.

Do Antiepileptic Drugs Increase the Risk of Suicide?

Psychiatric adverse events, including symptoms of depression and anxiety, have been reported with the use of several AEDs, particularly barbiturates (phenobarbital and primidone), topiramate, tiagabine, zonisamide, vigabatrin, and levetiracetam (20–23). The incidence of suicidal phenomena linked to specific AEDs has not been systematically or well studied. In fact, only one study could be found; it showed that 0.7% of patients exposed to levetiracetam reported suicidal ideation (21). In another observational study of 224 consecutive patients treated with levetiracetam, the drug was discontinued in four (1.8%) individuals because of episodes of major depression, with suicidal ideation. All four patients had a history of a depressive disorder (A.M. Kanner, MD, unpublished data, December 2006).

Suicidality seen with AED use, including phenobarbital (20), levetiracetam, (21), topiramate (22), tiagabine, and vigabatrin (23), occurs with the development of adverse psychiatric events in patients with a prior and/or family psychiatric history. Thus, these data may either reflect the natural course of an underlying recurrent psychiatric illness with no real effect from AEDs or could suggest that AEDs lower the threshold for manifesting psychiatric symptoms in individuals who are vulnerable because of a genetic or historical predisposition to psychiatric disorders. Furthermore, in some patients with pharmacoresistant epilepsy, psychiatric symptoms have resulted from the remission of seizures associated with the addition of an AED (23). This phenomenon, known as forced normalization, implies that the psychiatric symptoms are not the expression of AED toxicity.

In January 2008, the FDA issued an alert regarding the association between suicidality and AEDs, which was based on results of a meta-analysis that included data from 199 randomized clinical trials of 11 AEDs: carbamazepine, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, valproate, and zonisamide (6). The meta-analysis encompassed a total of 43,892 patients treated for epilepsy, psychiatric disorders, and other disorders, predominantly pain. The FDA concluded that there was a statistically significant 1.80-fold increased risk of suicidality with exposure to AEDs. Suicidality occurred in 4.3 per 1,000 patients treated with AEDs in the active arm, compared with 2.2 per 1,000 patients in the comparison arm. Of all the suicidality reported, suicidal ideation accounted for 67.6%, preparatory acts for 2.8%, attempts for 26.8%, and completed suicide for 2.8%. AEDs were associated with a greater risk for suicidality with epilepsy (OR, 3.53; 95% CI: 1.28–12.10) than with psychiatric disorders (OR, 1.51; 95% CI: 0.95–2.45) or other disorders (OR, 1.87; 95% CI: 0.81–4.76). Yet, the validity of the results of this meta-analysis recently have been questioned because of methodological problems, including (24):

1) The assessment of suicidality was based on "spontaneous" reports of patients, and the reports were not gathered in a systematic prospective manner.
2) The FDA associated the increased risk of suicide with all AEDs, despite the fact that statistical significance was found in only 2 (i.e., topiramate and lamotrigine) of the 11 AEDs studied. Furthermore, inclusion of three additional studies of lamotrigine resulted in the loss of statistical significance for this AED. Two other AEDs, valproic acid and carbamazepine, actually yielded a "small protective effect." The FDA's decision to present the risk as involving all AEDs stemmed from a concern that singling out specific AEDs might only change prescribing

practices, rather than emphasize the suicide risk. Clearly, their reasoning is not scientifically based.

3) Most epilepsy trials (92%) include patients on adjunctive therapy (compared with 14% of psychiatric trials and 15% of other medical trials). It is unclear whether the higher suicidality rates in the epilepsy trials were due to drug interactions, given the high proportion of epilepsy trials designed with polytherapy, or whether they potentially were due to the low suicidality risk associated with carbamazepine and valproate—both drugs are protective for suicidality and are the most common comparison drugs in these trials (25).
4) Suicidal behavior was greater in certain geographic regions. For example, the OR of suicidality was 1.38 (95% CI: 0.9–2.13) in North American studies and 4.53 (95% CI: 1.86–13.18) in studies done elsewhere. Such differences strongly suggest serious methodological errors in data gathering.

Clearly, the results of this meta-analysis must be considered with great caution at this time. In fact, only a study in which suicidality data are collected in a systematic and prospective manner can help determine whether a specific AED increases or decreases the risk. Yet, these data cannot be disregarded, since the FDA has decided to insert suicide warnings in the package inserts of all AEDs; thus, physicians will need to identify patients with increased risks of suicide.

How to Identify Patients at Risk?

Neurologists are not expected to manage the psychiatric disorders or the suicidal ideation or behavior of patients with epilepsy. Yet, they can be expected to identify the three most frequent risks associated with suicidality:

1) Current or past history of mood and anxiety disorders.
2) Family psychiatric history of mood disorders, particularly of suicidal behavior.
3) Past suicidal attempts.

Self-report screening instruments aimed at identifying major depressive episodes and generalized anxiety disorders are available and can be extremely helpful in assessing risk. These instruments include a six-item, self-rating screening, called the Neurological Disorders Depression Inventory for Epilepsy (NDDI-E), which was developed to identify major depressive episodes, specifically for people with epilepsy (26). None of its items can be confounded with adverse events of AEDs or cognitive symptoms associated with the seizure disorder or the underlying neurological insult that caused the epilepsy. The NDDI-E takes less than 3 minutes to complete; a score of 15 and higher is suggestive of a major depressive episode and serves as a red-flag referral to a psychiatrist for further evaluation.

No self-rating instrument to identify symptoms of generalized anxiety disorder has been validated for people with epilepsy. Yet, The Patient's Health Questionnaire, Generalized Anxiety Disorder-7 (GAD-7), can be extremely helpful (27). It is a seven-item, self-rating instrument that takes 3 minutes to complete; a score of greater than 10 is suggestive of a generalized anxiety disorder. Similarly, there are no self-rating instruments to assess a history of suicidality. So, the following six questions from the suicidality module of the Mini International Neuropsychiatric Interview (MINI) (28) are used to provide valuable information: 1) Have you ever made a suicide attempt? Questions 2 to 6 begin with, "In the past month." 2) Did you think you would be better off dead or wish you were dead? 3) Did you want to harm yourself? 4) Did you think about suicide? 5) Did you have a suicide plan? 6) Did you attempt suicide? Patients who answer positive to question 1, 3, or 4 are considered to have a moderately severe risk of suicide, whereas those who answer positive to question 5 or 6 or to both 1 and 4 are considered to be at high risk.

The identification of any current or past symptoms of depression, anxiety, and suicidality or a family history of these conditions is not considered a reason to delay the start of AED therapy, as the likelihood of seizure recurrence poses a greater safety risk for patients. Yet, AEDs known to increase the risk of psychiatric adverse events in vulnerable populations (barbiturates, levetiracetam, topiramate, zonisamide, and vigabatrin) are used with great caution.

In conclusion, the causes of suicidality for people with epilepsy are multiple, with prior or current psychiatric history and family psychiatric history being the most important risk factors. The degree to which AEDs cause an increased suicidal risk is not yet determined, and that assessment will require future studies that are methodologically sound. Nonetheless, caution must be used in patients with epilepsy and current or past psychiatric history.

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