Depression and Epilepsy: We Are No Longer One Direction

Association of Depression and Treated Depression With Epilepsy and Seizure Outcomes: A Multicohort Analysis.

Josephson CB, Lowerison M, Vallerand I, Sajobi TT, Patten S, Jette N, Wiebe S. *JAMA Neurol* 2017;74:533–539.

IMPORTANCE: A bidirectional relationship exists between epilepsy and depression. However, any putative biological gradient between depression severity and the risk of epilepsy, and the degree to which depression mediates the influence of independent risk factors for epilepsy, has yet to be examined. OBJECTIVE: To determine the effect of depression on the risk of epilepsy and seizure outcomes. DESIGN, SETTING, AND PARTICIPANTS: An observational study of a population-based primary care cohort (all patients free of prevalent depression and epilepsy at 18–90 years of age who were active after the Acceptable Mortality Reporting date in The Health Improvement Network database) and a prospectively collected tertiary care cohort (all patients whose data were prospectively collected from the Calgary Comprehensive Epilepsy Programme). The analyses were performed on March 16, 2016. MAIN OUTCOME AND MEASURES: The hazard of developing epilepsy after incident depression and vice versa was calculated. In addition, a mediation analysis of the effect of depression on risk factors for epilepsy and the odds of seizure freedom stratified by the presence of depression were performed. RESULTS: We identified 10,595,709 patients in The Health Improvement Network of whom 229,164 (2.2%) developed depression and 97,177 (0.9%) developed epilepsy. The median age was 44 years (interquartile range, 32–58 years) for those with depression and 56 years (interquartile range, 43–71 years) for those with epilepsy. Significantly more patients with depression (144,373 [63%] were women, and 84,791 [37%] were men; P < .001) or epilepsy (54,419 [56%] were women, and 42,758 [44%] were men; P < .001) were female. Incident epilepsy was associated with an increased hazard of developing depression (hazard ratio [HR], 2.04 [95% CI, 1.97–2.09]; P < .001), and incident depression was associated with an increased hazard of developing epilepsy (HR, 2.55 [95% CI, 2.49–2.60]; P < .001) There was an incremental hazard according to depression treatment type with lowest risk for those receiving counselling alone (HR, 1.84 [95% CI, 1.30–2.59]; P < .001), an intermediate risk for those receiving antidepressants alone (HR, 3.43 [95% CI, 3.37–3.47]; P < .001), and the highest risk for those receiving both (HR, 9.85 [95% CI, 5.74–16.90]; P < .001). Furthermore, depression mediated the relationship between sex, social deprivation, and Charlson Comorbidity Index with incident epilepsy, accounting for 4.6%, 7.1%, and 20.6% of the total effects of these explanatory variables, respectively. In the Comprehensive Epilepsy Programme, the odds of failing to achieve 1-year seizure freedom were significantly higher for those with depression or treated depression. CONCLUSIONS AND RELEVANCE: Common underlying pathophysiological mechanisms may explain the risk of developing epilepsy following incident depression. Treated depression is associated with worse epilepsy outcomes, suggesting that this may be a surrogate for more severe depression and that severity of depression is associated with severity of epilepsy.

Commentary

With humble apologies offered to anglophiles and pop music aficionados, we in clinical medicine can no longer accept a "one-direction" approach to the etiologies of depression and epilepsy. Josephson and colleagues have given us analyses from a large database for consumption, and in doing so, may have propelled us well past conventional wisdom characterizing epilepsy and psychiatric comorbidity and related severity of the two conditions. Initially, the authors have confirmed the findings of other large population based studies that have found bi-directional associations with epilepsy and psychiatric illness and/or suicidality (1-3). However, the study goes on to suggest that severity of depression may also be associated with the severity of epilepsy and vice versa.

We have long known that depression is more common in epilepsy than in other similarly encumbering diseases such as asthma or diabetes. The proposed reasons vary as to why this is so. Some consider that epilepsy leads to depression because, psychologically, patients may be compromised in their "locus of control" and have a variant of learned helplessness as a result (4). Yet seizure type may also matter. We have also learned in recent years to be alert that epilepsy localized in the temporal lobe may have a higher than expected presence of depressive symptoms (5, 6).

Depression resulting from epilepsy, either through psychosocial context or from functional neuroanatomy seems to be relatively well accepted by the field. However, the idea that

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depression may lead to the development of epilepsy presents an etiologic challenge that has not yet been resolved. For over a decade, we have heard about bi-directionality of depression and epilepsy (7). If both conditions are true, then notions of mental illness differing from "organic" illness must be revised. These are not new ideas, as a literal interpretation of the famous "epileptic and melancholia" quote by Hippocrates suggests that he considered depression and epilepsy closely related.

Josephson and colleagues may have given us notable evidence to help propel this bi-directional line of thinking even more into the limelight. The authors use a comprehensive database throughout the United Kingdom that included diagnoses and demographics from hundreds of medical practices. Timed incidences of diagnoses were recorded, so the questions of whether depression preceded epilepsy and vice versa could be aptly addressed. The results are compelling. Not only did people with epilepsy develop depression more often than those without epilepsy, but hazard ratios were increased for those with depression ultimately developing epilepsy.

Information was also available from a separate database from the Comprehensive Epilepsy Center in Calgary. Although this database was smaller than the UK sample, it was still sizeable enough to allow queries of bi-directionality with robust statistical power. Additional clinical detail was also available, particularly regarding the types of treatment received for depression—counseling alone, antidepressants, or both. The gradations of treatments could be reasonably considered as a proxy for the severity of the depressive illness. People with higher levels of treatment for depression were incrementally more likely to subsequently develop epilepsy. Not only did severity of depression predict a subsequent diagnosis of epilepsy, but current use of an antidepressant predicted less likelihood of having 1 year of seizure freedom. Essentially, severe depression appeared to be associated with more severe or medically refractory epilepsy.

Although the database used is comprehensive and appears to be detailed enough to allow the comparisons to be appropriately made, it is also true that depression is often under-recognized and undertreated. Depression identified in this sample was well below recognized prevalence of depression in the general population. If more depression was recognized and treated in this sample, the results could be somewhat different. The fact that incident depression in the face of epilepsy and incident epilepsy in the face of depression were identified even with the overall depression incidence so low makes the authors' case for bi-directionality even stronger.

Evidence supporting bi-directionality and related severity changes paradigms of brain function and etiology of neuropsychiatric illness as a whole. Conventional wisdom suggests that overlap of depression and epilepsy reflects comorbidity, that is, the intersection of two separate conditions. However, the comorbidity approach may be incorrect. The relationship between psychiatric illness and epilepsy may be more intimate than simple co-occurrence. Instead, the two conditions may be intertwined within the same pathophysiologic processes. Bi-directionality has credibility in other fields as well. Cardiac disease and depression seem to be bi-directional (8). If the heart's health depends upon mental health, then how can it be anything but intuitive to consider that the brain's health and stability is also dependent upon mental well-being.

The treatment implications are even more intriguing. If severe depression is associated with severe epilepsy, then it will be difficult to disregard the idea that treating depression is a potential strategy to improving epilepsy outcomes. Although the study was done in adults, one wonders what implications are present in a pediatric population. Given this new evidence of bi-directionality, it is not farfetched to consider that treating a young person with either epilepsy or depression may then improve the long-term vulnerability for yet undiagnosed depression and epilepsy respectively. Years ago, such views were considered wildly speculative, but with a new paradigm for etiology of neuropsychiatric illness, these notions may be closer to fact than originally thought. Thanks to Josephson and colleagues, our etiologic thinking regarding severity of associated depression and epilepsy may no longer be limited to one direction.

by Jay Salpekar, MD

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