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Depression and Epilepsy: The Bidirectional Relation Goes On and On…

Directionality of the Association Between Epilepsy and Depression: A Nationwide Register-Based Cohort Study

Bølling-Ladegaard E, Dreier JW, Kessing LV, Budtz-Jørgensen E, Lolk K, Christensen J. *Neurology*. 2023;100(9):e932-e942. doi:10.1212/WNL.0000000000201542. Epub 2022 Nov 22.

Background and objectives: Epilepsy and depression share a bidirectional relationship; however, its magnitude and long-term temporal association remain to be elucidated. This study investigates the magnitude and long-term association between epilepsy and depression, comparing with the risks of the 2 disorders after another chronic medical illness (asthma). Methods: In a nationwide register-based matched cohort study, we identified all individuals who received a first diagnosis of epilepsy, depression, and asthma from January 1, 1980, to December 31, 2016. We used a Cox regression model to estimate the risk of epilepsy after depression and vice versa and the risk of epilepsy or depression after asthma, compared with healthy references matched on age and sex, adjusting for medical comorbidity, substance abuse, and calendar time. Results were stratified by epilepsy subtype. We furthermore investigated the risk of admission with acute seizures for persons with epilepsy who became depressed. Results: In a population of 8,741,955 individuals, we identified 139,014 persons with epilepsy (54% males, median age at diagnosis 43 years [inter quartile range (IQR) 17-65 years]), 219,990 persons with depression (37% males, median age at diagnosis 43 years [IQR 29-60 years]), and 358,821 persons with asthma (49% males, median age at diagnosis 29 years [IQR 6-56 years]). The adjusted hazard ratio (aHR) of depression after epilepsy was 1.88 (95% CI 1.82-1.95), and the aHR of epilepsy after depression was 2.35 (95% CI 2.25-2.44). The aHR of depression after asthma was 1.63 (95% CI 1.59-1.67) and that of epilepsy after asthma, 1.48 (95% CI 1.44-1.53). The risk of depression was highest in the few years preceding and after an epilepsy diagnosis, and vice versa, but remained elevated during the entire follow-up period for both directions of the association. There was no evidence of a stronger association with depression for any epilepsy subtype. Receiving a diagnosis of depression subsequent to an epilepsy diagnosis was associated with a 1.20-fold (95% CI 1.07-1.36) increased HR of acute hospital admission with seizures. Discussion: We identified a long-term bidirectional relationship between depression and epilepsy in a large-scale cohort study. Risk estimates were higher than those of epilepsy or depression after asthma.

Commentary

Depression has been recognized as a common epilepsy comorbidity for decades, and evidence has mounted in recent years that various poor outcomes are associated with comorbid depression, including poor quality of life, increased mortality, increased healthcare costs, increased adverse effects, and potentially worsened epilepsy severity.[1] While initially it seemed intuitive that individuals with epilepsy were at risk for developing depression in response to social stressors and other key life changes accompanying epilepsy diagnosis, treatment, and the unpredictability of seizures, subsequent epidemiology research indicated the association was not so simple. In fact, studies demonstrated depression risk increases *before* seizure onset among individuals later diagnosed with epilepsy, and individuals with depression are at increased risk for epilepsy.[2,3] This bidirectional relation between epilepsy and depression was elegantly demonstrated in a rigorous study by Hesdorffer et al. which evaluated incidence rate ratios for depression in the 3 years prior to and following epilepsy diagnosis among a matched UK General Practice Research Database cohort.[4] Significantly increased, close to 2-fold incidence of depression was demonstrated in each of the 3 years prior to and after diagnosis of epilepsy, compared to matched controls. While this study provided robust evidence of a bidirectional association, limitations included lack of data examining time frames before and after the 6-year window surrounding epilepsy diagnosis and lack of a chronic disease control group analyzed in a similar manner to epilepsy. This was important, since presence of one condition such as epilepsy or depression could introduce bias toward increased

recognition of other conditions, due to more frequent healthcare system contact.

Bølling-Ladegaard and colleagues conducted a rigorous population-based analysis which directly addressed these methodological gaps in prior literature, by examining Danish nationwide inpatient register data over a 36-year period and including comparison analyses among an asthma cohort.[5] Over 36 years of follow-up, the authors identified separate cohorts of all individuals with a new diagnosis of epilepsy, depression, or asthma along with 5 sex and age-matched controls. Hazard ratios were calculated during follow-up for depression after an epilepsy diagnosis, epilepsy after a depression diagnosis, and separately for depression or epilepsy after an asthma diagnosis. Indeed, the analyses demonstrated increased risk of depression after epilepsy (adjusted hazard ratio, aHR 1.88 compared to controls) and increased risk of epilepsy after depression (aHR 2.35 compared to controls). These magnitudes of association were both greater than the risk of epilepsy or depression after asthma, with no overlap in confidence intervals between the epilepsy and asthma analyses. Further, findings demonstrated that increased risk for depression in epilepsy and vice versa was present throughout the 36-year time frame, though risk tended to be highest in the years just prior to and following epilepsy or depression diagnosis, respectively. An additional analysis examining rate of acute hospitalization for seizures demonstrated increased risk of hospitalization for seizures among those with epilepsy who developed depression (aHR 1.20).

Limitations of these analyses include some validity concerns for the Internationl Classification of Diseases (ICD)-based diagnoses analyzed in the national registers, lack of more detailed information to explore individual risk factors for co-occurrence of epilepsy and depression, and the use of hospital-based codes, which did not capture outpatient diagnoses. This may have biased the findings toward lower estimates, especially with regard to milder cases not requiring hospital care. This limitation and the overall use of population-based healthcare diagnostic information may have underestimated the magnitude of association, especially with regard to depression after epilepsy, given robust evidence demonstrating psychiatric comorbidities including depression are often under-detected in people with epilepsy in the absence of systematic evaluation.[6] Also, since hospital-based diagnoses often arise after disease onset and potentially after an initial outpatient diagnosis, the timing of diagnoses in the analysis do not uniformly represent true disease onset.

Despite these limitations, the results of this investigation have significant implications for next research steps, as well as clinical care. First, the results lend further support to the existence of a common underlying pathophysiology of epilepsy and depression. Evidence exists to support potential genetic contributions, as well as potential roles of neurotransmitter systems, disturbances in structure or function of particular brain regions, dysfunction of the hypothalamic-pituitary axis or other endocrine dysfunction, and inflammatory disturbances.[7-9] Further elucidation of these common underlying pathophysiologies is critical, as a better understanding could set the stage for novel and potentially disease-modifying therapies targeting appropriate mechanisms. As current management of depression and epilepsy typically involves separate pharmacotherapy approaches that are largely symptomatic, elucidating shared mechanisms and evaluating novel common therapy targets could bring a fruitful paradigm shift to the field. Other targets for future research should include characterizing the bidirectional relation further among epilepsy and other psychiatric comorbidities, to clarify the scope of the association across multiple psychiatric conditions and consider common mechanisms and potential treatment approaches across these different psychiatric phenotypes. Current evidence suggests that these bidirectional associations are present for multiple psychiatric conditions,[4] though the most robust evidence is for depression.

Finally, and perhaps most importantly, the findings of Bølling-Ladegaard and colleagues have direct implications for current clinical practice. The increased risk for depression after epilepsy throughout follow-up supports current efforts including quality measures for ongoing screening in epilepsy care at every visit.[10] Further, the higher risk around the time of epilepsy diagnosis suggests a need for special attention to screening and management early in epilepsy care. New onset epilepsy patients may thus be a good target group for potential gradual introduction of integrated mental healthcare services in epilepsy centers. The increased risk of hospitalization for seizure among those with epilepsy and depression suggests a potential need for closer follow-up or more proactive care delivery to people with epilepsy and depression. Greater attention to this higher-risk group of patients may help prevent hospitalizations, identify and address drug-resistant epilepsy sooner, and potentially improve outcomes. Future research would also be important to evaluate if clinical action such as early intervention for depression in epilepsy reduces hospitalizations and improves other outcomes.

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Declaration of Conflicting Interests

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