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Anti-Seizure Medications on Trial Again: Accused of Parkinson's Disease!

Association Between Antiepileptic Drugs and Incident Parkinson Disease

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Importance: Recent studies have highlighted an association between epilepsy and Parkinson disease (PD). The role of antiepileptic drugs (AEDs) has not been explored. Objective: To investigate the association between AEDs and incident PD. Design, setting, and participants: This nested case-control study started collecting data from the UK Biobank (UKB) in 2006, and data were extracted on June 30, 2021. Individuals with linked primary care prescription data were included. Cases were defined as individuals with a Hospital Episode Statistics (HES)–coded diagnosis of PD. Controls were matched 6:1 for age, sex, race and ethnicity, and socioeconomic status. Prescription records were searched for AEDs prescribed prior to diagnosis of PD. The UKB is a longitudinal cohort study with more than 500 000 participants; 45% of individuals in the UKB have linked primary care prescription data. Participants living in the UK aged between 40 and 69 years were recruited to the UKB between 2006 and 2010. All participants with UKB-linked primary care prescription data (n = 222 106) were eligible for enrollment in the study. Individuals with only a self-reported PD diagnosis or missing data for the matching variables were excluded. In total, 1477 individuals were excluded; 49 were excluded due to having only self-reported PD, and 1428 were excluded due to missing data. Exposures: Exposure to AEDs (carbamazepine, lamotrigine, levetiracetam, and sodium valproate) was defined using routinely collected prescription data derived from primary care. Main outcomes and measures: Odds ratios and 95% CIs were calculated using adjusted logistic regression models for individuals prescribed AEDs before the first date of HES-coded diagnosis of PD. Results: In this case-control study, there were 1433 individuals with an HES-coded PD diagnosis (cases) and 8598 controls in the analysis. Of the 1433 individuals, 873 (60.9%) were male, 1397 (97.5%) had their race and ethnicity recorded as White, and their median age was 71 years (IQR, 65-75 years). An association was found between AED prescriptions and incident PD (odds ratio, 1.80; 95% CI, 1.35-2.40). There was a trend for a greater number of prescription issues and multiple AEDs being associated with a greater risk of PD. Conclusions and relevance: This study, the first to systematically look at PD risk in individuals prescribed the most common AEDs, to our knowledge, found evidence of an association between AEDs and incident PD. With the recent literature demonstrating an association between epilepsy and PD, this study provides further insights.

Commentary

We are fortunate because we live in an era where we have many anti-seizure medications (ASM) to choose from to treat epilepsy. One of the factors that influence the selection of a specific ASM is its side effect profile. The short-term side effect profile is usually well established while long-term side effects are often not apparent and need time to be identified. We also must remember that we are still using medications that not only target the epileptic focus but also impact the nonepileptic regions in the brain and influence other body organs. Not surprisingly, studies have already linked chronic exposure to drugs like phenytoin to concerning side effects such as cerebellar atrophy, and peripheral neuropathy. There are also concerns regarding chronic exposure to enzyme-inducing medications being linked to osteoporosis and increased cardiovascular risk.[1] Patients and physicians are always on alert for new findings regarding ASMs, and it can be quite anxiety provoking when new side effects are identified. Anti-seizure medications as a class have been accused of increased suicidality,[2] premature cardiac death,[3] increased risk of dementia,[4] and now Parkinson's disease (PD). The headlines were concerning: "Epilepsy Drugs May Up Risk of Parkinson's" and "Antiepileptic Drugs Linked to Parkinson's Disease." Let us examine the evidence behind this latest accusation.

In their case-control study analyzing data from the UK Biobank, Belete et al[5] investigated whether exposure to ASMs

increased the risk of PD. Only patients from the UK Biobank who had linked primary care data were included. The cases consisted of patients having a hospital episode statistics International Classification of Diseases (ICD) code consistent with PD who were matched to 6 controls for year of birth, sex, socioeconomic status, race, and ethnicity. They then identified exposure to ASMs by identifying any ASM prescription prior to the first diagnostic code for PD. They evaluated the number of prescriptions filled, and whether the patient was on monotherapy or polytherapy. They identified 1433 cases with PD, 97.5% white, of whom 62 (4.3%) were previously exposed to an ASM compared to 2.5% from the control group. The most commonly prescribed medications were carbamazepine (32), lamotrigine (15), levetiracetam (12), and valproic acid (30). The odds ratio for developing PD when compared to controls was 1.8 (95% Confidence Interval (CI) 1.35-2.4), with significant odds ratios for lamotrigine, levetiracetam, and valproic acid. Findings remained significant when excluding ASM exposure up to 5 years prior to the PD diagnosis. When adjusting for a diagnosis of epilepsy, or using a more stringent criteria for the outcome (PD diagnosis + 2 prescriptions of a dopaminergic agent), only valproic acid remained significantly linked to an increased odds of developing PD. The odds ratio (OR) also increased with polytherapy exposure and among those with a higher number of prescriptions. The authors concluded that there is an association between lamotrigine, levetiracetam, valproic acid, and PD and that the association is most robust for valproic acid.

The motivation for this study was the finding that epilepsy increased the odds of PD, based on analysis of the UK Biobank cohort from the same group.[6] The question for this study was whether the link between epilepsy and PD was mediated by ASMs. Before delving into the data for each individual drug, it would be helpful to discuss the limitations of the methodology. The first issue that comes to mind is that the exposure group was quite limited; we are talking about only 62 individuals in the PD group, with the most common exposure being carbamazepine at 32. Another issue is the accuracy of the diagnostic codes; these codes were not entered by neurologists so a patient with drug-induced tremors could have easily been classified as having PD. This becomes evident when looking at the more stringent outcome of PD and 2 prescribed dopaminergic medications because with this definition the exposure to ASMs drops from 62 to 29, and only the valproic acid relationship remains. The authors also mention the possibility that epilepsy patients were more likely to have hospital admissions compared to those without, thus increasing the likelihood of them being diagnosed with other disorders including PD. Another significant limitation was the lack of control for comorbid mood disorders, psychotic disorders, and prior exposure to antidopaminergic agents. Epilepsy patients are at increased risk of bipolar disorder and psychosis. Bipolar disorder has been linked with an increased risk of PD[7] and is often treated with dopamine antagonists which can also increase the risk of PD.

If we examine each drug through the lens of reproducibility and biological plausibility, we find the association between levetiracetam, lamotrigine, and PD to be unexpected. In fact, a recent study also looking at this question by analyzing German primary care practices found valproic acid to be significant while the other 2 drugs were not.[8] Levetiracetam has even been suggested as a treatment for PD due to leucine-rich repeat kinase 2 mutations.[9] Lamotrigine on the other hand has been described to cause reversible drug-induced parkinsonism,[10] but there are no other reports linking it to PD or to PD-related pathophysiological mechanisms. The most suspicious culprit seems to be valproic acid at this point. Reversible drug-induced parkinsonism has been described in epilepsy cohorts in 2.5% of the cases.[11] It is also one of the main reasons to obtain a DaT scan to differentiate between PD and drug-induced PD because the features of both conditions can look very similar.[12] Valproic acid has many mechanisms of action some beneficial and some deleterious including mitochondrial dysfunction, GABAergic modulation, histone deacytlase inhibition, and fatty acid metabolism.[13] It is possible that one of the mechanisms of action affects dopaminergic pathways and can lead to PD, although some animal models of PD have shown neuroprotective effects for valproic acid.[14]

So what judgment should the jury pass on these drugs? I do not believe that based on the evidence so far, there should be a concern for levetiracetam or lamotrigine causing PD. However, valproic acid's track record remains a concern and its teratogenic effects have already led to physicians avoiding this drug in women of childbearing age. It remains, however, a very effective medication for generalized epilepsy and has beneficial mood stabilizing properties. Given this, we should try to collect further evidence to determine whether we are placing patients at risk by exposing them to valproic acid, and whether the changes are irreversible. A guilty verdict remains premature, but at least we have a lead suspect.

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Declaration of Conflicting Interests

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