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Review Article

Antiepileptic Drugs and Parkinson's Disease: A Meta-Analysis of Existing Evidence

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Abstract:

Background. There is growing interest in the association between antiepileptic drugs (AEDs) exposure and subsequent Parkinson's disease (PD).

Methods. We conducted a literature search in the PubMed, SCOPUS, and Web of Science databases. We identified studies using an observational design and performed a meta-analysis to evaluate the association between AEDs exposure and incident PD. We assessed the quality of the studies and identified the pooled odds ratio (OR) for those exposed to AEDs compared to those who were not.

Results. Of the 1,775 unique studies identified, 55 were selected for full-text review. Five studies (n = 127,324) were included. Quality assessment revealed moderate-to-high methodological quality in the studies included. The overall OR for a PD was 1.82 (95% CI: 1.35-2.45) in AEDs recipients. When considering each drug individually, the magnitude of association was highest for valproate (OR 3.94, 95% CI: 3.15-4.92) and lowest for carbamazepine (OR 1.32, 95% CI: 1.16-1.49). Further interaction tests revealed higher odds for lamotrigine than for carbamazepine and valproate than for carbamazepine and lamotrigine.

Conclusion. This study revealed potential associations between AEDs and incident PD. However, existing evidence remains insufficient, making it premature to draw inferences on this matter.

Keywords: Antiepileptic Drugs; AEDs; Antiseizure Medications; Epilepsy; Parkinson's Disease

Introduction

Neurological disorders represent an area of particular interest, given their pronounced contribution to global disability estimates (1, 2). Epilepsy and Parkinson's disease (PD) are among the most prevalent chronic conditions and are both associated with an increased disability burden worldwide (3). Despite advances in treatment and a better understanding of disease progression, the exact pathophysiological mechanisms remain unclear (4, 5).

Despite the lack of a genetic correlation between epilepsy and PD (6), the existing literature suggests a bidirectional association (7) and possible shared mechanisms (8). Recent studies have revealed a temporal relationship between these conditions (9, 10); however, it is challenging to explore the contribution of antiepileptic drugs (AEDs) to PD due to insufficient data on medication history. Although AEDs are mostly used for seizure treatment, their prescriptions frequently go beyond this (11). Hence, AEDs may account for some association between epilepsy and PD, highlighting the need for further research.

Studies on PD risk factors have become an important research topic over the last few decades. Despite existing evidence on the temporal relationship between epilepsy and PD, it remains unclear whether epilepsy or its treatment contributes to an elevated risk of PD. Thus, the relationship between AEDs exposure and subsequent diagnosis of PD is of growing interest. Currently, there is an increasing number of observational studies in this field that lack critical summaries. Recognizing the rising interest and existing literature gap, we conducted a meta-analysis to evaluate the association between AEDs exposure and incident PD.

Methods

Overview and outcome measure

This meta-analysis was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (12) and was registered with PROSPERO (CRD42024603543). This analysis focused on studies conducted in diverse clinical settings and geographical locations, involving patients taking AEDs for various conditions and not limited to epilepsy. The outcome of interest was incident PD-specific symptom episodes confirmed through hospital episode statistics in patients exposed to AEDs compared to those who were not taking AEDs. This association was expressed as odds ratios (OR).

Literature search

Two reviewers (RA and DK) examined the titles, abstracts, and full texts of all potentially eligible publications with the assistance of a third reviewer (RK) using broad criteria to allow the inclusion of any potentially relevant study for further evaluation. The authors conducted a comprehensive literature search in three bibliographic databases: PubMed (1953–2024), Scopus (1987–2024), and Web of Science (1993–2024) on October 23, 2024, using combinations of the terms "antiseizure drugs," "antiepileptic drugs," "parkinsonism," and "Parkinson's disease," without restrictions on language or publication date. Eligible studies included original research examining the association between AEDs exposure and parkinsonism or PD. Full details of the search strategy are provided in the Appendix (Supplemental Table 1). Additionally, we manually searched the reference lists of the included papers and individually identified articles on the topic to identify additional eligible studies.

Table 1. Characteristics of included studies.

Authors (year)	Study type	Study entry period	Sample size (total)	Data source	Country	Age range at study entry	AED prescription diagnoses (ICD codes)	Outcome	Confounders
Hwang et al., (2024)	Matched cohort study	2002-2013	10,510	National Health Insurance	South Korea	Between the ages	Epilepsy (G40), status epilepticus (G41), Landau-	PD	Age, Sex, economic status, residential area, body Mass

(13)				Service Health Screening Cohort		of 40 and 79 years	Kleffner syndrome (F803), convulsion (R56)		Index, smoking, drinking, hypertension, type 2 diabetes mellitus, ischemic heart disease, congestive heart failure, traumatic brain injury, central nervous system
Belete et al. (2023) (14)	Nested case-control study	1990 - 2008	10,031	UK Biobank	UK	Between the ages of 40 and 69 years	NA	PD	Epilepsy, race and ethnicity
Kostev et al. (2023) (15)	Matched case-control study	2010-2021	49,900	IQVIA Disease Analyzer database	Germany	≥18 years	Epilepsy (G40), restless legs syndrome (G25.8), diabetic/toxic/drug-induced neuropathy (G62, E10.4, E11.4, E14.4)	PD	NA
Zhang et al. (2023) (16)	Nested case-control study	NA	6,174	Electronic health primary care records in East London	UK	NA	NA	PD	Age, sex, ethnicity, index of multiple deprivation, and epilepsy diagnosis
Skow et al. (2013) (17)	Matched case-control study	1990-2008	50,709	UK General Practice Research Database	UK	NA	NA	PD	Body mass index, smoking status, alcohol consumption, use of calcium channel blockers, annual consultation rate

Selection of studies

Full-text articles were assessed for inclusion by two reviewers (RA and DK). Studies were included if they involved patients exposed to AEDs, reported the occurrence of PD, or presented PD-associated symptoms confirmed by clinical assessment, medical records, or databases with a stated diagnosis following AEDs exposure. Articles were excluded if they met any of the following criteria: no reports on PD, case series, case reports, brief reports, editorials, letters, reviews, studies lacking clear reporting on the outcome of interest, studies not specifically reporting on exposure, and studies performed in animals. Detailed information on the excluded studies is provided in the Appendix (Supplemental Table 2). The quality of the studies was assessed using the Newcastle-Ottawa Scale (NOS). All studies

were independently rated by DK and DA and checked by RK to resolve any disagreements.

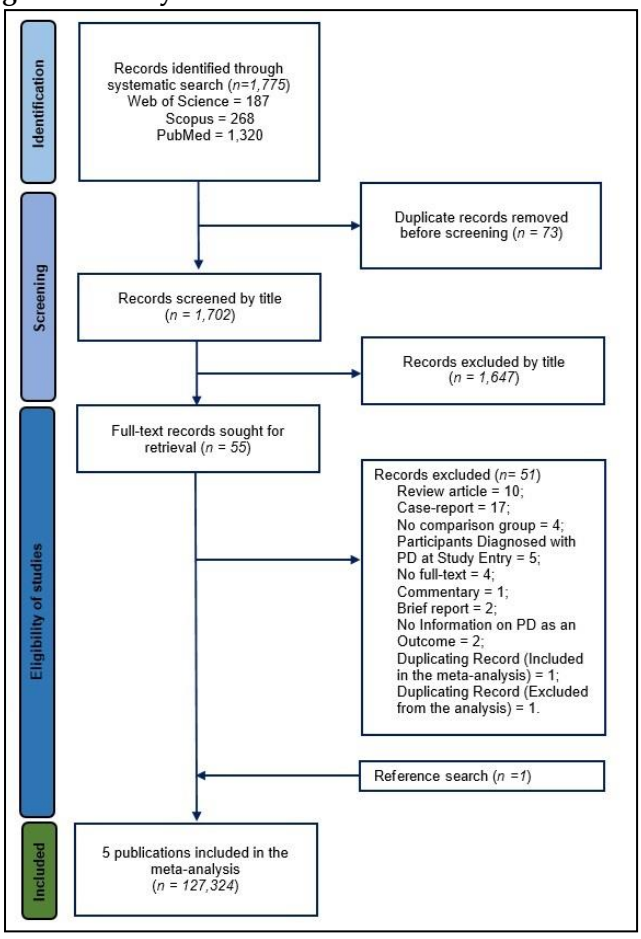
Statistical analysis

We developed a standardized data extraction form using Microsoft Office software. For the full-text publications included, two reviewers (RA and DK) separately retrieved and cross-checked the data, including research details, participant characteristics, and data required to compute pooled ORs. Furthermore, we extracted data on incident PD and stratified them according to AEDs type (if such data were available). A meta-analysis was performed using random-effects models, and 95% confidence intervals (95% CIs) were reported. We calculated heterogeneity estimates for the pooled estimates using the I^2 statistic and determined their significance using the Cochran's Q test p-value. We provided funnel plots, and their asymmetry was examined using Egger's regression tests to identify small study biases. To account for the family wise error, we incorporated a Bonferroni correction for multiple comparisons as α/n, where α and n are the significance level and the number of comparisons conducted within a specific (subgroup) meta-analysis, respectively. All statistical analyses were performed using STATA (V18).

Results

The literature search identified 1,775 studies. After eliminating duplicates, we examined 1,702 distinct citations to determine their eligibility criteria. Of these, 55 abstracts and full-text publications were examined, and five distinct studies (13-17) were found to be suitable for the meta-analysis (Figure 1).

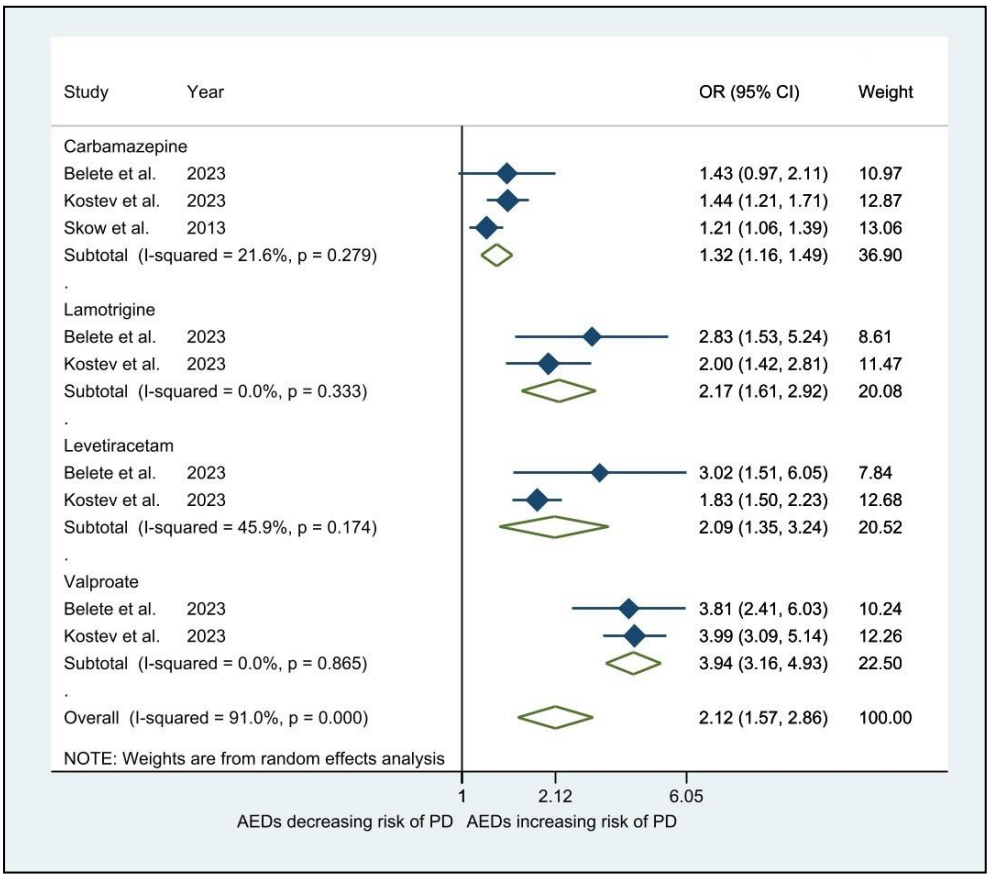
Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram of the systematic search.



These studies included 127,324 participants. All studies were registry-based; three were matched case-control studies, and the remaining two were nested case-control studies (Table 1). The publication years ranged from 2013 to 2024, and the studies were mostly from the UK (n=3), followed by Germany (n=2) and South Korea (n=2). In the meta-analyzed literature, ratings for the risk of bias assessment varied from 6 to 9, indicating moderate-to-high methodological quality (Supplemental Table 3).

The overall OR for incident PD was 1.82 (95% CI: 1.35-2.45; p <0.001) (Figure 2, Supplemental Figure 1). The pooled ORs indicated substantial variability in the effect size (I2 = 94.70%; Q <0.001). However, further examination of the funnel plot did not suggest a small study bias (Egger's test, p=0.71), which demonstrated a symmetrical distribution of studies around the pooled OR, suggesting that the effect sizes were not influenced by study size or precision. Additional meta-analysis by drug types (Figure 3, Supplemental Figure 2) revealed the highest association for valproate (OR 3.94, 95% CI: 3.15-4.92; p <0.001), followed by levetiracetam (OR 2.09, 95% CI: 1.35-3.24; p <0.001), lamotrigine (OR 2.17, 95% CI: 1.61-2.92; p <0.001), and carbamazepine (OR 1.32, 95% CI: 1.16-1.49; p <0.001). Further pairwise comparisons revealed evidence of differences for all comparisons except levetiracetam vs. lamotrigine at the conventional significance level. However, when adjusting for multiple comparisons, three contrasts were found below the corrected significance level, suggesting higher odds for lamotrigine than for carbamazepine and for valproate than for carbamazepine and lamotrigine (Supplemental Table 4).

Figure 3. A subgroup meta-analysis of incident PD (by AEDs type).



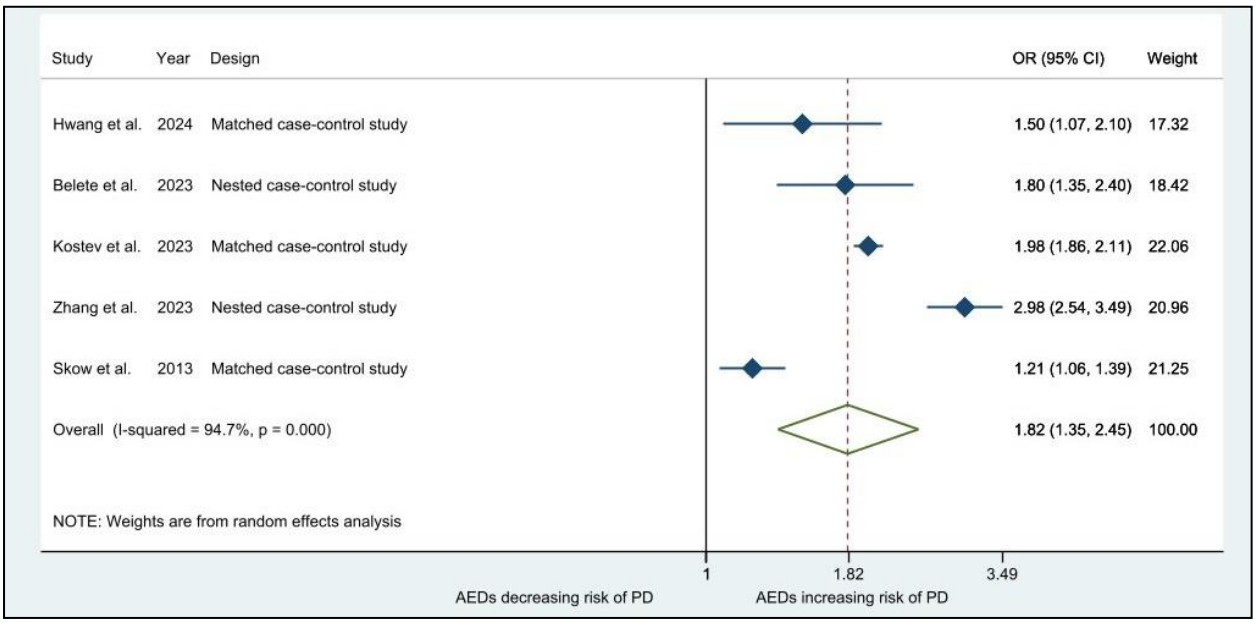
One study was published in a conference meeting and was not available in full text (16). Although it provided a sufficient amount of information, we tried to exclude it; however, the estimates remained mostly unchanged (Supplemental Figures 3 and 4). Neither subgroup analysis by study design decreased the heterogeneity estimates (Supplemental Figure 5). Both these additional analyses revealed substantially overlapping estimates, with the interaction test revealing p-values of 0.56 and 0.18, respectively, suggesting homogeneity of estimates.

Discussion

We conducted a comprehensive literature review and meta-analysis of the existing studies to evaluate the association between AEDs exposure and incident PD. The findings of our study revealed that odds of PD diagnosis was 1.82 (95%CI 1.35-2.45) times higher in the AEDs population than in those who were not taking AEDs. This suggests that patients on AEDs are more likely to be diagnosed with PD than their counterparts not taking AEDs. Although we were unable to define the causal mechanisms, these findings emphasize the importance of monitoring neurological symptoms in patients undergoing long-term AED therapy. When considering each drug individually, lamotrigine showed higher odds than carbamazepine, as did valproate compared with carbamazepine and lamotrigine. These findings are consistent with those of previous studies (18, 19).

Our final analysis included five distinct publications in which the sign and magnitude of the association between AEDs and PD were consistent across the studies. However, we observed large heterogeneity (94.7%), which might call into question the reliability of the estimand. However, this might be due to a statistical artifact: the sample sizes of the included studies were notably large, implying that uncertainty decreases as the estimate becomes more precise. Hence, I^2 becomes larger, irrespective of the true differences between the studies. This is evident in Figure 2, where the individual ORs ranged between 1.21 and 2.98, with all studies consistently reporting increased odds.

Figure 2. Forest plot of the association between AEDs exposure and risk of incident PD.



On the other hand, although it is encouraging to highlight these findings, it is worth noting that all studies were registry-based and lacked data on temporality. Additionally, the underlying reasons for prescribing AEDs in the study population were diverse in nature. Furthermore, participants in the comparison group (those who were unexposed to AEDs) were not necessarily drug naïve; they may have been taking other medications to manage various neurological disorders. This means that even though we compared those exposed to AEDs with those who were unexposed, this does not necessarily mean that the unexposed group did not take other drugs. This complicates our understanding of the role of AEDs in the development of PD. Finally, the accuracy of PD diagnosis remains a challenge, particularly during the early stages of PD (20), and may contribute to the discrepancies observed in effect size and heterogeneity.

To date, most studies analyzing the impact of AEDs on the onset of PD have focused on structural and biochemical processes (21, 22). These findings suggest that AEDs exert their effects by suppressing dopamine receptors and pathways. For example, certain AEDs, particularly valproic acid, enhance the inhibition of GABA activity in the brain (23). However, in the pathophysiology of PD, activation of the GABAergic system in the primary motor cortex may play a neuroprotective role and improve disease (24). Nevertheless, a more in-depth explanation of the association between AEDs and PD is required. A known hereditary predisposition to PD suggests a panel of genes associated with a high risk of PD, including LRRK2, GBA1, PRKN, SNCA, PINK1, PARK7, and VPS35(25). Additionally, genetic factors influence the development of PD, and epigenetic modifications regulate gene expression (26). A recent study demonstrated the role of epigenetic involvement in PD pathogenesis (27). These epigenetic changes (methylation, histone acetylation, and non-coding RNAs) occur because of environmental factors (28). Drugs can also be considered as external factors that influence gene expression as part of epigenetic mechanisms (29). Some studies have suggested that drug-induced PD is associated with hereditary predispositions (30). Although existing evidence remains scarce, we speculate that these processes may contribute to the association between AEDs and PD development.

In contrast, one study focused on the potential of carbamazepine to reduce the risk of PD (17). This idea came from studies that showed that carbamazepine can help initiate intracellular disposal pathways, which then cause misfolded proteins to be broken down by autophagy (19). Misfolded α-synuclein protein is also involved in the pathophysiology of PD (31). Some studies have speculated on the potential neuroprotective effects of carbamazepine in an ischemic/hypoxic model of neuronal injury (32).

The duration of AEDs exposure, its combination, and dosage may be correlated with the onset of PD. However, one study (17) showed little evidence of a dose- and duration-dependent association between AEDs and PD. Longitudinal studies observing patients over prolonged periods could reveal whether chronic

exposure to AEDs increases the risk of developing PD. Acknowledging the role of genetic factors in the association between AEDs and PD, future research should consider Mendelian randomization to fully understand the relationship between AEDs and PD. Further research could prove or disprove the association between prescription AEDs and the development of PD by examining more closely the ways in which AEDs may affect dopaminergic pathways and cause PD. Additionally, examining genetic predispositions and epigenetic modifications in patients using AEDs can aid in identifying biomarkers that can potentially predict susceptibility to PD. Considering that some studies in this meta-analysis did not include AEDs prescription diagnoses, it is important to examine how these conditions (epilepsy, neuralgia, bipolar disorder, and so forth) interact with AEDs exposure to influence the risk of developing PD.

Limitations

Our study had several limitations. The findings of this meta-analysis were based on observational studies. Although the association between AEDs and subsequent PD was consistent across studies, variability in follow-up, comorbidity load, medication adherence, duration of AEDs exposure, environmental factors, and genetic predispositions may have affected the outcome of interest. Co-occurring neuropsychiatric conditions are common in patients with epilepsy. Such interplay warrants clinical attention and etiological investigations to uncover the shared underpinnings and sources of vulnerability associated with AEDs and PD. Improved consistency in reporting illness loads and patterns of co-occurrence in future primary studies will provide further insights. Finally, although we attempted to encompass all existing evidence, our findings are exploratory and require further confirmation. Alternative approaches could be applied to include additional predictors to estimate this associations.

Conclusion

This study provides a critical summary of studies exploring the association between AEDs and incident PD. Our meta-analysis revealed 1.82 times increased odds of PD in AEDs recipients. However, the existing evidence is insufficient to definitively establish this association. Further research is required to investigate this relationship in a more rigorously controlled environment.

Supplementary Materials

Supplementary file available via:

Acknowledgments

Author Contributions: Conceptualization: A.SS., R.A., and G.K.; methodology and data curation: D.K., D.A., R.A.; formal analysis: D.K. and D.A.; writing – original draft preparation: R.A., G.K.; writing – review and editing; A.SS., R.K., and D.K.; and supervision: A.SS..

Data availability statement: Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

Statement of Ethics: The study approval was not required, since this was a meta-analysis of published studies.

Conflict of Interest Statement: The authors declare that they have no competing interests.

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