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Prescription trends and psychiatric symptoms following first receipt of one of seven common antiepileptic drugs in general practice

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ABSTRACT

We sought to examine the risk of psychiatric symptoms associated with a first prescription for specific antiepileptic drugs (AEDs) used in monotherapy in a general cohort of patients with epilepsy. We used The Health Improvement Network database (comprising the years 2000–2012) to identify incident patients with epilepsy. The index date was that on which they met the case definition for epilepsy, and analyses only included patients who remained on monotherapy or received no AED therapy following diagnosis to avoid confounding by polytherapy. Psychiatric symptoms were defined using mental health clinical or treatment (medical or therapeutic) code. We analyzed the AED of interest as a time-varying covariate in multivariate Cox proportional hazard regression models controlling for confounding factors. We identified 9595 patients with incident epilepsy, 7400 of whom (77%) received a first-recorded AED prescription. Prescriptions for newer generation AEDs (lamotrigine and levetiracetam) steadily increased (constituting over 30% of all AED prescriptions by 2012) while valproate use significantly declined in females (~40% in 2002 to just over 20% by 2012). A total of 2190 patients were first exposed to carbamazepine (29.3%) and 222 to lamotrigine (3%), both of which were associated with a lower hazard of any coded psychiatric symptom or disorder in multivariate analyses (hazard ratio [HR]: 0.84, 95% confidence interval [95% CI]: 0.73–0.97; p = 0.02 and HR: 0.83, 95% CI: 0.70–0.99; p = 0.03, respectively, for carbamazepine and lamotrigine). Carbamazepine was also associated with a lower hazard for depression (HR: 0.81; 95% CI: 0.69–0.96; p = 0.013) and anxiety (HR: 0.77; 95% CI: 0.63–0.95; p = 0.013) in secondary analyses. This study provides evidence that carbamazepine and lamotrigine are associated with lower hazards for psychiatric symptoms following a diagnosis of epilepsy. These estimates can be used in clinical settings, and the precision should improve with more contemporary data that include larger proportions of newer generation AEDs.

1. Introduction

Psychiatric disorders are common in people with epilepsy. Approximately 23% of patients with epilepsy have active depression [1]. Furthermore, the odds of reporting anxiety and suicidal thoughts are 2.4-fold (95% confidence interval [95% CI]: 1.5–3.8) and 2.2-fold (95% CI: 1.4–3.3) higher, respectively, in people with epilepsy compared with the general population [2]. Not surprisingly, psychiatric comorbidities are also a major determinant of quality of life in those with epilepsy [3].

In addition to comorbidities, antiepileptic drugs (AEDs) themselves can unmask subclinical psychiatric disorders or elicit *de novo* affective symptoms [4]. In particular, there is evidence that in select populations with epilepsy, levetiracetam, clobazam, barbiturates, and phenytoin are associated with a variety of psychiatric adverse effects that include affective disorders, psychosis, and irritability/aggression [5].

Prior studies using data from large administrative and electronic medical records (EMR) have typically focused on AEDs as a class, rather than as individual medications, or examined their association with a limited range of conditions focusing primarily on the association

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between overall AED use and suicidal behavior [6–8]. There is a relative paucity of evidence examining the risk of psychiatric symptoms related to specific AEDs. Therefore, the purpose of this study was to address the risk of a composite outcome of any psychiatric symptom (stratified by subtypes) attributed to individual AEDs following a first-ever prescription using large, primary care data collected during routine care.

2. Methods

2.1. The Health Improvement Network

The Health Improvement Network (THIN) database is an EMR data platform of anonymized primary care patients. The patients are derived from general practice (GP) clinics that constitute approximately 5% of the UK population. These patients are broadly representative of the general population [9]. All medical events are coded using Read codes [10] and include specialist evaluations and emergent medical care records that are routinely sent to the patient's GP clinic. Prescription data are recorded by the GP clinicians, coded by the UK Prescription Pricing Authority, and classified by the British National Formulary [11,12]. Missing data are imputed using a twofold fully conditional specification algorithm [13]. We used THIN version 1205 and restricted the timeframe to January 1, 2000 to May 31, 2012 since 2000 was the year in which levetiracetam, the newest of the seven studied AEDs, was approved.

2.2. Study population

To increase the chance of identifying an incident cohort of patients with epilepsy, we used a modified version of a published case definition designed specifically for THIN [14] using a conventional five-year washout period. The published definition requires a single Read code for an epilepsy syndrome or two Read codes for symptoms of epilepsy (*i.e.*, codes for nonfebrile seizures on two or more occasions) and two AED codes within 4 months and is 92% accurate for detecting cases of pediatric epilepsy [14]. Our modified definition only differs from the published version by omitting the necessity for AED codes. This was decided *a priori* to isolate the additional hazard associated with a single AED in monotherapy compared with no treatment following an incident diagnosis of epilepsy. This case definition has recently been validated for identifying adults with epilepsy (sensitivity = 86% [95% CI: 80%–91%]; specificity = 97% [95% CI: 92%–99%]) in the Secure Anonymised Information Linkage (SAIL) Databank, a similarly constructed Welsh EMR database [15].

To mitigate the risk of immortal time bias, we required all patients to be active in the database after the Acceptable Mortality Reporting date (the date when mortality reporting was considered complete) for each individual practice [16]. We increased the chance of excluding prevalent cases of epilepsy by using a five-year washout period from enrollment to first epilepsy code. We then compared those with and without a psychiatric code at any point over the five or more years of follow-up prior to meeting the EMR epilepsy phenotype. A history of psychiatric symptom or treatment was defined using medical and therapeutic Read and Multilex codes (medication codes that are assigned by First Databank and are linked directly to the British National Formulary). This definition of a psychiatric outcome, as well as subsets of psychiatric events, was reached through a consensus-driven process between two authors (CBJ and SP; Appendix 1). Finally, we excluded any patient receiving an AED over at least 5 years prior to the index date and those receiving two or more AEDs at any point during follow-up to isolate the unique effects of each specific medication used in monotherapy. All patients aged 18 years or greater at epilepsy diagnosis who met these conditions were included in the analysis.

2.3. Statistical analysis

The index date (time zero) was that on which the patient met our case definition for epilepsy. A code for first AED prescription was treated as the exposure. We required that first AED prescriptions occur after the year 2000 (the year levetiracetam, the newest of the seven evaluated AEDs, was approved by the European Medicines Agency). We then followed patients for two years after the first AED prescription. The primary exposure was the first AED prescription. We divided follow-up into four 6-month periods. Exposure to each AED was recorded as a dichotomous ("yes"/"no") time-varying covariate during each 6-month epoch, based on the presence or absence of a prescription record during that time period. We then determined whether a person had a psychiatric code during each epoch. The patient was considered to have incurred the outcome of interest (any code for a psychiatric sign, symptom, or disorder as listed in Appendix 1) during the epoch in which they were coded for the adverse effect. Otherwise, patients were censored at the end of the 24-month analysis period, loss to follow-up, or death if no outcome occurred.

Descriptive statistics were used to compare populations of interest. Time-varying Cox proportional hazards regression analysis was used to estimate the hazard of a psychiatric adverse event following a putative first-ever prescription for an AED in monotherapy. Goodness of fit was determined using the concordance statistic (C statistic). All models controlled for age at index date, sex, a history of a psychiatric code (defined as the presence of any psychiatric code listed in Appendix 1 from inception in the GP until the day prior to the index date), baseline Charlson comorbidity index [17], and the Townsend index of social deprivation [18]. All these potential confounders have been independently associated with presumed incident depression in patients with epilepsy identified in THIN [19]. We considered a p-value of ≤0.05 to be statistically significant.

2.4. Secondary analyses

We anticipated that prescription patterns for certain AEDs would change over time and that this may be sex-dependent [20,21]. Hence, we evaluated unique AED prescriptions as a percentage of total AED prescriptions each year from January 1, 2000 to May 31, 2012. We compared proportions from the beginning and end of the study period stratified by sex and between sexes in the year 2012. We subsequently evaluated the risk of subsets of psychiatric symptoms and disorders. We categorized psychiatric codes into depression, anxiety, psychosis/mania, and suicidal ideation/completed suicide. A prescription for an antidepressant was counted as both a depression and anxiety event since we were unable to determine the reason for prescription, and depression and anxiety are often intermixed. A prescription for an antipsychotic medication was classified as a psychosis/mania outcome.

2.5. Software

All analyses were conducted using Hive 0.13.1, R version 3.1.2 [22], and Python 2.7 [23].

2.6. Ethics

The Health Improvement Network has been used for scientific research since approval from the NHS South-East Multi-Centre Research Ethics Committee in 2003. Ethics approval for this study was obtained both through the University of Calgary's Conjoint Health Research Ethics Board (REB15-0203) and the CMD Medical Research's Scientific Review Committee in December 2015 (SRC Reference number 15THIN087).