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Co-Morbidity and Medication Profiles of Patients with Epilepsy and Matched Controls in US and UK Electronic Health Records Systems

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1. Introduction

The global burden of epilepsy is substantial, especially in the developing regions of the world where treatments are less accessible (de Boer et al., 2008). One contribution to the overall disease burden is the higher prevalence of comorbidities among patients with epilepsy, compared to the general population. These include psychological comorbidities, such as depression, which have been associated with epilepsy, both before and after epilepsy diagnosis (Hesdorffer et al., 2005). Other neurological diseases such as migraine have also been associated with epilepsy (Ottman & Lipton, 1994).

Two database studies were utilised to assess the overall comorbidity profiles of patients with epilepsy and matched controls without epilepsy. The analyses allow for comparisons between the relative prevalence estimates of comorbidities within populations captured through electronic health data sources. The US Impact National Managed Care Benchmark Database (IHCIS) is an insurance claims database provided by Ingenix, Eden Prairie, MN, and the UK General Practice Research Database (GPRD) Gold contains electronic medical records and is managed by the Medicines and Healthcare products Regulatory Agency.

The IHCIS database contains medical (inpatient, outpatient, physician, and ancillary) and pharmacy claims from a national sample of 46 managed care health plans covering approximately 93 million lives over the period 1997 to 2009.

The GPRD Gold is the world's largest computerised database of anonymised longitudinal medical records from primary care (Jick et al., 2003). The data are drawn from the computer systems used by general practitioners (GPs) to maintain the clinical records within their practices, and contain all records that primary care deemed relevant to patient care. Currently, data are available from 561 "research standard" general practices throughout the UK, providing information from 4.0 million currently registered patients (c. 9.0 million in total).

The objectives of the current analyses were: (1) to calculate the prevalence of epilepsy diagnosis in a US and a UK electronic health record system, stratified by gender and age

category; (2) to describe and compare the prevalence of co-morbidities, in epilepsy patients and matched controls without any record of epilepsy; and (3) to describe the prevalence of medication use by epilepsy patients during a one-year period of observation.

2. Methods

This study was a case-control study comparing comorbidities between patients with epilepsy and matched controls without epilepsy, and a descriptive study reporting medication use among patients with epilepsy.

2.1 Patient population
2.1.1 Case selection
The definitions of active epilepsy reflected the structure of the databases and how medical and pharmacy data are captured:

In IHCIS, epilepsy cases were identified based on at least two records of epilepsy on or before the index date and with 30 days or more between the first and last record of epilepsy. At least one of the records of epilepsy had to be recorded within the lead-in period to identify individuals with recently active epilepsy. Epilepsy was defined as the ICD-9 code 345*, with * indicating all terms under this hierarchy. AED treatment was not part of the case definition of epilepsy in the IHCIS in order to capture epilepsy patients in the claims database that may not have pharmacy benefits. Also, disease diagnoses are recorded on a regular basis in the insurance claims, therefore a repeat diagnosis could be used to confirm the epilepsy diagnosis.

In the GPRD, epilepsy cases were identified as those with one epilepsy diagnosis (READ) code on or before the index date. The relevant GPRD medical codes were identified and reviewed by a clinician. Within the GPRD, active epilepsy cases were required to have at least 2 anti-epileptic drug (AED) prescriptions within -3 and +6 months of any epilepsy diagnosis code AND at least 1 AED prescription within the lead-in or analysis period. In the GPRD, a diagnosis is often recorded only one time on the database therefore the medications were used as a proxy to confirm the diagnosis and that the diagnosis was still active near the time of the index date.

Full definitions of index date, analysis and lead-in periods are provided in Section Data Analysis.

2.1.2 Control selection
Controls were matched to cases at a ratio of 1:1 by: gender, exact year of birth, duration of prior continuous enrolment in the database (from index date) by the following categories (1-<2 years, 2-<3 years, 3-<4 years, 4 or more years).

For IHCIS specifically, controls were also matched on pharmacy benefits throughout the full analysis period (Yes/No), Mental Health benefits on the index date (Yes/No/Partial), and Provider/Plan Type (on the index date).

For GPRD specifically, the controls were also matched by General Practice site.

2.2 Data analysis
The analysis period was defined as the 12 month period from 01/Jan/2009 to 31/Dec/2009, inclusive. The first day of the analysis period (01/Jan/2009) was assigned as the "index

date" for cases and their matched controls. The pre-analysis lead-in period was defined as the 12 month period from 01/Jan/2008 to 31/Dec/2008, inclusive. Thus, the study inclusion period contains all time from 01/Jan/2008 to 31/Dec/2009, inclusive.

A base population was defined containing all patients eligible for this study. This was the denominator for calculations of the population prevalence of epilepsy. All cases and controls were selected from this population.

For inclusion in the base population, a patient must have been:

- registered on the database for the full lead-in period to allow the identification of existing epilepsy patients.
- registered on the database for the full analysis period to allow the characterisation of patients' current medication and comorbidities.
- aged between 0 and 120 years inclusive, on the index date

For the IHCIS, the analyses of medication use were restricted to those cases with full pharmacy benefits throughout the analysis period and no gaps in pharmacy benefit greater than one day during the analysis period.

2.2.1 Analysis 1: prevalence of epilepsy

The prevalence of epilepsy on the index date was determined, by gender and age category, as appropriate. The denominator was taken as all patients within the base population. In IHCIS, the numerator was calculated as all patients (within the denominator population) with two or more records of epilepsy, and 30 days or more between the first and last record of epilepsy. In GPRD, the numerator was calculated as all patients (within the denominator population) with an epilepsy diagnosis prior to the index date, and at least 2 anti-epileptic drug (AED) prescriptions within -3 and +6 months of any epilepsy diagnosis code AND at least 1 AED prescription within the lead-in or analysis period. For both databases, at least one of the diagnoses must be on, or before, the index date.

2.2.2 Analysis 2: listing of comorbidities in epilepsy patients

The prevalence of comorbidities within the epilepsy and control populations was determined. A patient was considered to have a comorbidity if they had one or more records of this condition within the time period being considered. Prevalence of comorbid disease in the epilepsy population was calculated as the number of epilepsy cases with a record of the disease (within the time periods defined below) divided by the total number of epilepsy cases. Prevalence of comorbid diseases in the controls were similarly calculated. Analyses were repeated for two time periods, (1) the analysis period and (2) the analysis period, and any time before, within the period of continuous enrollment.

In GPRD, the comorbidities are listed as defined by disease headings which were based on the Meddra Dictionary and were reviewed by clinicians. A Read/MedDRA (version 13.0) mapping was created using the available Read/MedDRA (version 6) dictionary and the 2010-AB release of the Unified Medical Language System (UMLS). Approximately 41% of events were not mapped, but many of the events remaining unmapped were not of clinical significance. Some of these were mapped by further review of terms.

In IHCIS, comorbidities are reported by Clinical Classifications Software (CCS) level 4 (HCUP, 2011).

In addition, there were a number of conditions previously associated with epilepsy that were specifically explored including: depression, anxiety, bipolar disorder, suicidality, and migraine. These conditions were defined by clinician-reviewed coding lists using GPRD GOLD READ medical codes or ICD-9 codes for IHCIS.

In GPRD, medications are listed as defined by British National formulary (BNF) class, and in IHCIS by Universal System Classification (USC) Fourth Level. The USC is a categorization system, developed by IMS, to resolve a need for therapeutic classification of pharmaceutical products; the USC is widely accepted in North America as the standard for pharmaceutical product classification.

2.2.3 Analysis 3: comparative analyses of the occurrence co-morbidities

The relative prevalence of co-morbidities in epilepsy cases and matched controls was assessed. Unstratified matched analyses were conducted via conditional logistic regression using the SAS Proc PHREG procedure. Stratified analyses were conducted via the Fisher Exact tests using the SAS Proc FREQ procedure. Odds ratios (ORs) and 95% confidence intervals are presented (Note: p-values are not presented). Since these were exploratory (rather than hypothesis testing) analyses, and sample sizes are not based on statistical considerations, there was no adjustment for multiple testing. ORs are only presented where there were at least five patients in both the case and control populations with a record of the comorbidity within the time period being considered. Results are presented for the 25 most frequent comorbidities amongst cases, and for the 25 highest ORs comparing cases and controls.

2.2.4 Analysis 4: listing of prescribed medications used by epilepsy cases during a one-year period of observation

The prevalence of drug use within the analysis period is presented for the epilepsy population. A patient was considered to be using the drug of interest if they were issued a prescription during the analysis period. The prevalence of drug use was calculated as the number of eligible cases with a record of use within the analysis period divided by the total number of eligible cases. Results are presented for cases only, and reported at Universal System Classification Fourth Level.

3. Results

There were 27,328 active epilepsy cases and 27,328 matched controls identified in the UK GPRD, and 83,045 active epilepsy cases and 83,045 controls identified from the IHCIS. Active epilepsy in GPRD was defined if a patient diagnosed with epilepsy had at least one AED prescription within the one-year lead-in or one-year analysis period. Active epilepsy in the IHCIS was defined if the patient had at least one diagnosis code within the lead-in or analysis period. The overall prevalence of active epilepsy was 0.8% in GPRD and 0.5% in IHCIS. The prevalence in GPRD increased with age and was highest in the age group 65 years and older. The prevalence was similar across the age groups in IHCIS with a peak of 0.5% in the age group 45 to 64 years.

The studies within the US claims database (IHCIS) and UK general practice database (GPRD) compared the prevalence of a range of psychiatric conditions including anxiety,

bipolar disorder, depression, schizophrenia/psychosis and suicidality (Table 1&Table 2). These psychiatric conditions were significantly more common in epilepsy cases than in controls (OR > 1.0, and lower bound of 95% CI excluding 1.0). The highest ORs were for suicidality, bipolar disorder and schizophrenia. Migraine was also included in the analyses, and it was significantly more common among cases than controls for the time period during or before analysis period. However, the association was not significant for the analysis period only in GPRD, and the associations were stronger in IHCIS than GPRD. Given the chronic nature of these conditions the prevalence was considered both during and prior to the analysis period (i.e. the latter period represented the patients' medical histories).
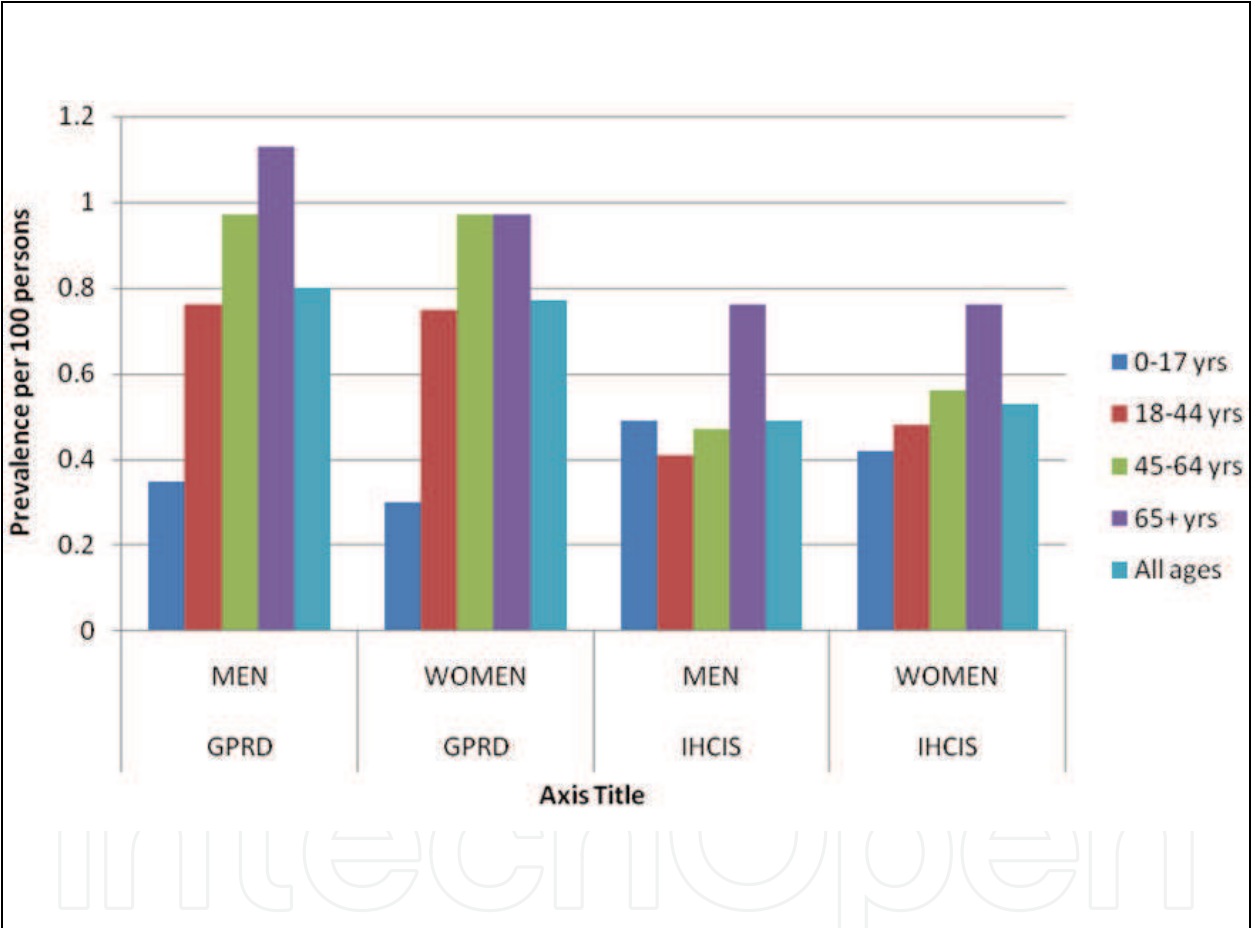

Fig. 1. The prevalence of active epilepsy per 100 persons on 1st January 2009 in the GPRD and IHCIS databases, stratified by age and sex

The top 25 most common diagnosed comorbidities among cases are reported for within the analysis period (Table 3 & Table 7) and within the analysis period or before (Table 4 & Table 8), for GPRD and IHCIS respectively. As expected, the medical condition headings related to epilepsy, seizures and convulsions were at the top of the lists. Other conditions included respiratory infections, skin conditions, and hypertension. The latter conditions were also common in controls.

The top 25 diagnosed comorbidities with the highest ORs comparing cases to controls were reported for the analysis period (Table 5 & Table 9) and within the analysis period or before (Table 6 & Table 10), for GPRD and IHCIS respectively. These listings can be considered for generating hypotheses about the associations between epilepsy and other conditions, though temporality cannot be established.

In the GPRD, mental retardation had a high OR of 24.9 (95%CI: 12.3-50.4) during the analysis period. During the GPRD analysis period, the conditions with the highest ORs included many neurological conditions and behaviour and socialisation disturbances (Table 5). In the GPRD analysis period or ever before, the conditions with the highest ORs also included neurological and developmental conditions, and the highest ORs were 50.7 (95%CI: 28.0-92.1) for "Cerebral disorders congenital", 38.1 (95%CI: 20.9-69.3) for "Congenital and peripartum cerebral disorders", and 33.9 (95%CI: 16.8-68.4) for "Neonatal neurological system disorders NEC" (Table 6).

The highest OR in the IHCIS was for intellectual disabilities, 143.1 (95%CI: 84.6-241.9) during the analysis period, and 79.8 (95%CI: 60.1-106.1) during the analysis period or ever before. The other conditions with high ORs included neurological disorders, cerebrovascular disease, developmental and learning disorders, and mental disorders (Table 9 & Table 10).

Medication use was reported for the analysis year, 2009, for epilepsy cases only (N=27,328 GPRD; N= 46,912 IHCIS). For IHCIS, only individuals with full pharmacy benefits throughout the year 2009 were included in medication analyses. The proportion of patients using anti-depressants and anti-epileptic drugs were reported using clinician-reviewed drug coding lists (Table 11 & Table 13). In the GPRD, 97% of the epilepsy cases had a prescription for an anti-epileptic drug in the analysis period, as expected since AED use either in the lead-in or analysis period was a requirement of the case definition (3% of cases only had AED use in the lead-in period). Eighteen percent of cases had a prescription for anti-depressants in the one-year analysis period. In the IHCIS, 76% of epilepsy patients had a prescription for an AED, and 22% for anti-depressants in 2009. The 24% of epilepsy cases who did not have an AED in the analysis period may either not have had pharmacy benefit, or they were not prescribed an AED in that time period. However, the relative proportions of patients using each type of AED are of interest, and there are differences in the AED use between the UK GPRD and US IHCIS. Two of the older AEDs, valproate (34%) and carbamazepine (32%) were the most frequently used AEDs among epilepsy patients in the GPRD, followed by lamotrigine (18%) and phenytoin (17%). Lamotrigine (15%) and phenytoin (15%) were the most commonly used AEDs in the IHCIS in 2009, followed by carbamazepine (12%) and topiramate (9%).

The top 25 most commonly prescribed medication categories in a one year time period, 2009, are reported for GPRD (Table 12) and IHCIS (Table 14). As in (Table 11), drugs classified as "Control of Epilepsy" were the most commonly prescribed in GPRD (97.3%). Other common medications were neuropathic pain (52.3%), non-opioid analgesics (39.7%), anti-manic drugs (32.4%), non-steroidal anti-inflammatory drugs (30.2%), opioid analgesics (23.8%), broad spectrum penicillins (21.1%), and statins (20.2%). In the IHCIS, 74% of epilepsy patients had a prescription in the "Seizure disorders" drug category during 2009. The other frequently prescribed medications were codeine (23%), extended spectrum macroli (19%), benzodiazepines (17%), and selective serotonin reuptake inhibitors (SSRI, 15%).

Comorbidity	GPRD					IHCIS	
	Number Cases	Percent Cases	Number Controls	Percent Controls	Odds Ratio (95% CI)	Number Cases	Percent Cases
Anxiety	750	2.74	677	2.48	1.1 (1, 1.2)	9354	11.26
Bipolar Disorder	26	0.1	7	0.03	3.7 (1.6, 8.6)	2029	2.44
Depression	1207	4.42	1034	3.78	1.2 (1.1, 1.3)	9696	11.68
Migraine	188	0.69	173	0.63	1.1 (0.9, 1.3)	5806	6.99
Schizophrenia (GPRD)/ Psychosis (IHCIS)	20	0.07	5	0.02	4.0 (1.5, 10.7)	2215	2.67
Suicidality	76	0.28	20	0.07	3.8 (2.3, 6.2)	1389	1.67

Suicidality = Suicide attempts, probable suicide attempts and suicidal ideation
CI= Confidence interval; GPRD= General Practice Research Database; IHCIS= Integrated Healthcare Information Services

Table 1. Prevalence and odds ratios for the comorbidities of interest comparing cases (N=27,328 GPRD; N=83,045 IHCIS) and controls (N=27,328 GPRD; N=83,045 IHCIS) during the analysis period

	GPRD					IHCIS	
Comorbidity	Number Cases	Percent Cases	Number Controls	Percent Controls	Odds Ratio (95% CI)	Number Cases	Percent Cases
Anxiety	5858	21.44	4544	16.63	1.4 (1.3, 1.5)	21214	25.55
Bipolar Disorder	217	0.79	97	0.35	2.3 (1.8, 2.9)	3829	4.61
Depression	7988	29.23	6196	22.67	1.5 (1.4, 1.5)	19762	23.8
Migraine	2378	8.70	1841	6.74	1.3 (1.3, 1.4)	13557	16.32
Schizophrenia (GPRD)/ Psychosis (IHCIS)	299	1.09	108	0.40	2.8 (2.3, 3.6)	7299	8.79
Suicidality	1011	3.70	378	1.38	2.8 (2.5, 3.1)	4877	5.87

Suicidality = Suicide attempts, probable suicide attempts and suicidal ideation
CI= Confidence interval; GPRD= General Practice Research Database; IHCIS= Integrated Healthcare Information Services

Table 2. Prevalence and odds ratios for the comorbidities of interest comparing cases (N=27,328 GPRD; N=83,045 IHCIS) and controls (N=27,328 GPRD; N=83,045 IHCIS) during or ever before the analysis period

Comorbidity	Number Cases	Percent Cases	Number Controls	P C
Social issues	4276	15.65	3527	1
Musculoskeletal and connective tissue pain and discomfort	3751	13.73	3196	1
Coughing and associated symptoms	3607	13.20	2728	9
Upper respiratory tract infections NEC	3112	11.39	2693	9
Upper respiratory tract infections	3111	11.38	2693	9
Joint related signs and symptoms	2826	10.34	2405	8
Seizures and seizure disorders NEC	2638	9.65	11	0
Dietary and nutritional therapies	2441	8.93	1977	7
General signs and symptoms NEC	2313	8.46	1482	5
Reproductive organ and breast histopathology procedures	2262	8.28	2499	9
Lower respiratory tract and lung infections	1946	7.12	1138	4
Lower respiratory tract infections NEC	1936	7.08	1125	4
Non-site specific injuries NEC	1548	5.66	876	3
Pain and discomfort NEC	1450	5.31	1116	4
Bronchospasm and obstruction	1444	5.28	1128	4
Neurological signs and symptoms NEC	1429	5.23	764	2
Dermatitis and eczema	1400	5.12	1076	3
Urinary tract infections	1349	4.94	754	2
Asthenic conditions	1343	4.91	862	3
Gastrointestinal and abdominal pains (excl oral and throat)	1318	4.82	1092	4
Vascular hypertensive disorders NEC	1207	4.42	1381	5
Oral soft tissue infections	1174	4.30	973	3
Bladder and urethral symptoms	1135	4.15	683	2
Gastrointestinal atonic and hypomotility disorders NEC	1128	4.13	598	2
Headaches NEC	1079	3.95	751	2

CI= Confidence Interval; GPRD= General Practice Research Database, NEC= Not elsewhere classified

Table 3. Prevalence and odds ratios for the top 25 most common comorbidities comparing cases and controls during the analysis period in the GPRD

Comorbidity	Number Cases	Percent Cases	Number Controls	Percent Controls
Seizures and seizure disorders NEC	26225	95.96	279	1.02
Social issues	17790	65.10	16830	61.59
Upper respiratory tract infections NEC	16529	60.48	15504	56.73
Upper respiratory tract infections	16529	60.48	15504	56.73
Musculoskeletal and connective tissue pain and discomfort	15299	55.98	14339	52.47
Coughing and associated symptoms	13657	49.97	11438	41.85
General signs and symptoms NEC	12478	45.66	8900	32.57
Joint related signs and symptoms	12153	44.47	10691	39.12
Dietary and nutritional therapies	11088	40.57	10941	40.04
Non-site specific injuries NEC	10949	40.07	7931	29.02
Dermatitis and eczema	10442	38.21	8736	31.97
Lower respiratory tract and lung infections	10357	37.90	7734	28.30
Lower respiratory tract infections NEC	10326	37.79	7709	28.21
Reproductive organ and breast histopathology procedures	9986	36.54	10502	38.43
Pain and discomfort NEC	8849	32.38	7585	27.76
Oral soft tissue infections	8693	31.81	8108	29.67
Gastrointestinal and abdominal pains (excl oral and throat)	8637	31.60	7805	28.56
Asthenic conditions	8219	30.08	5825	21.32
Neurological signs and symptoms NEC	7933	29.03	4404	16.12
Skin structures and soft tissue infections	7823	28.63	5654	20.69
Headaches NEC	7733	28.30	5677	20.77
Cardiac signs and symptoms NEC	7544	27.61	5307	19.42
Allergies to foods, food additives, drugs and other chemicals	7499	27.44	6002	21.96
Depressive disorders	7177	26.26	5660	20.71
Urinary tract infections	7098	25.97	5133	18.78

CI= Confidence Interval; GPRD= General Practice Research Database, NEC= Not elsewhere classified

Table 4. Prevalence and odds ratios for the top 25 most common comorbidities comparing cases and controls during or before the analysis period in the GPRD

Comorbidity	Number Cases	Percent Cases	Number Controls	Percent Controls
Seizures and seizure disorders NEC	2638	9.65	11	0.04
Mental retardations	199	0.73	8	0.03
Withdrawal and rebound effects	46	0.17	5	0.02
Disability issues	277	1.01	33	0.12
Abnormal behaviour NEC	47	0.17	6	0.02
Sodium imbalance	156	0.57	20	0.07
Pervasive developmental disorders NEC	44	0.16	6	0.02
Behaviour and socialisation disturbances	197	0.72	29	0.11
Calcium metabolism disorders	35	0.13	6	0.02
Cerebellar coordination and balance disturbances	50	0.18	8	0.03
Therapeutic bladder catheterisation	109	0.40	20	0.07
Lower respiratory tract inflammatory and immunologic conditions	35	0.13	6	0.02
Nervous system therapeutic procedures NEC	66	0.24	12	0.04
Salivary gland disorders NEC	49	0.18	9	0.03
Confusion and disorientation	179	0.66	38	0.14
Cortical dysfunction NEC	199	0.73	43	0.16
Thoracic cage fractures non-spinal (excl pathological)	32	0.12	7	0.03
Thoracic cage fractures and dislocations	32	0.12	7	0.03
Schizophrenia NEC	22	0.08	5	0.02
Bipolar disorders	26	0.10	6	0.02
Psychiatric elimination disorders	42	0.15	10	0.04
Tremor (excl congenital)	223	0.82	57	0.21
Nervous system haemorrhagic disorders	31	0.11	8	0.03
Delusional symptoms	23	0.08	6	0.02
Drug withdrawal therapies	33	0.12	9	0.03

Comorbidity	Number Cases	Percent Cases	Number Controls	Perc Cont
Seizures and seizure disorders NEC	26225	95.96	279	1.02
Cerebral disorders congenital	559	2.05	11	0.04
Congenital and peripartum cerebral disorders	419	1.53	11	0.04
Neonatal neurological system disorders NEC	271	0.99	8	0.03
Nervous system neoplasms unspecified malignancy NEC	365	1.34	11	0.04
Meningiomas benign	240	0.88	11	0.04
Hydrocephalic conditions	345	1.26	18	0.07
Mental retardations	1342	4.91	87	0.32
Traumatic central nervous system haemorrhages	191	0.70	13	0.05
Cerebrovascular embolism and thrombosis	59	0.22	5	0.02
Developmental disorders cognitive	377	1.38	28	0.10
Vascular anomalies congenital NEC	171	0.63	12	0.04
Leukopenias NEC	69	0.25	5	0.02
Paralysis and paresis (excl cranial nerve)	1458	5.34	114	0.42
Encephalopathies NEC	154	0.56	12	0.04
Congenital eye disorders NEC	137	0.50	11	0.04
Disability issues	2277	8.33	212	0.78
Pervasive developmental disorders NEC	495	1.81	44	0.16
Nervous system haemorrhagic disorders	977	3.58	85	0.31
Anterior pituitary hypofunction	86	0.31	8	0.03
Cerebrovascular aneurysms and dissections	75	0.27	7	0.03
Behaviour and socialisation disturbances	2575	9.42	308	1.13
Inborn errors of amino acid metabolism	73	0.27	14	0.05
Antidiuretic hormone related conditions	71	0.26	8	0.03
Central nervous system aneurysms	61	0.22	7	0.03

Comorbidity	Number Cases	Percent Cases	Number Controls	Perc Con
Epilepsy	45635	54.95	0	0
Convulsions	41078	49.46	9	0.01
Other connective tissue disease	25108	30.23	16519	19.8
Essential hypertension	24367	29.34	19961	24.0
Immunizations and screening for infectious disease	23827	28.69	20398	24.5
Disorders of lipid metabolism	23526	28.33	21045	25.3
Other and unspecified lower respiratory disease	20413	24.58	12854	15.4
Symptoms, signs and ill-defined conditions	20263	24.40	9946	11.9
Other non-traumatic joint disorders	18437	22.20	12774	15.3
Other skin disorders	18071	21.76	14957	18.0
Other and unspecified upper respiratory infections	17051	20.53	14692	17.6
Other nervous system symptoms and disorders	15474	18.63	4413	5.31
Malaise and fatigue	13586	16.36	7983	9.61
Other upper respiratory disease	12762	15.37	9794	11.7
Abdominal pain	11910	14.34	7637	9.20
Other eye disorders	11335	13.65	8142	9.80
Other injuries and conditions due to external causes	11228	13.52	4945	5.95
Depressive disorders	10907	13.13	4801	5.78
Other central nervous system disorders	10826	13.04	2403	2.89
Nonspecific chest pain	10769	12.97	6747	8.12
Acute upper respiratory infections of multiple or unspecified sites	10722	12.91	8206	9.88
Other headache	10462	12.60	4132	4.98
Other and unspecified gastrointestinal disorders	10127	12.19	5516	6.64
Other bone disease and musculoskeletal deformities	9909	11.93	7073	8.52
Other thyroid disorders	9886	11.90	6979	8.40

Comorbidity	Number Cases	Percent Cases	Number Controls	Percent Controls
Convulsions	76929	92.64	58	0.07
Epilepsy	69782	84.03	0	0
Other connective tissue disease	50298	60.57	36898	44.43
Other and unspecified lower respiratory disease	46270	55.72	31447	37.87
Other non-traumatic joint disorders	42216	50.84	31641	38.10
Other skin disorders	41651	50.15	34760	41.86
Other and unspecified upper respiratory infections	41109	49.50	36734	44.23
Other nervous system symptoms and disorders	37912	45.65	11592	13.96
Disorders of lipid metabolism	37001	44.56	32157	38.72
Malaise and fatigue	35255	42.45	21419	25.79
Essential hypertension	33858	40.77	27249	32.81
Other upper respiratory disease	33727	40.61	26344	31.72
Abdominal pain	32829	39.53	23175	27.91
Other injuries and conditions due to external causes	32800	39.50	16637	20.03
Nonspecific chest pain	31341	37.74	20177	24.30
Acute upper respiratory infections of multiple or unspecified sites	30716	36.99	24805	29.87
Other headache	30126	36.28	13070	15.74
Allergic reactions	28909	34.81	22971	27.66
Other eye disorders	28567	34.40	21219	25.55
Other and unspecified gastrointestinal disorders	27635	33.28	17061	20.54
Superficial injury; contusion	26869	32.35	15552	18.73
Other ear and sense organ disorders	26352	31.73	18559	22.35
Other and unspecified circulatory disease	25911	31.20	15087	18.17
Other central nervous system disorders	25633	30.87	4591	5.53
Sprains and strains	25339	30.51	20144	24.26

Comorbidity	Number Cases	Percent Cases	Number Controls	Percent Controls	C...
Convulsions	41078	49.46	9	0.01	1
Intellectual disabilities	2010	2.42	17	0.02	1
Cancer of brain and nervous system	1705	2.05	43	0.05	3
Developmental disabilities	1312	1.58	45	0.05	3
Other paralysis	3942	4.75	116	0.14	3
Congenital hip dislocation	217	0.26	9	0.01	2
Other nervous system congenital anomalies	864	1.04	34	0.04	2
Learning disorders	1792	2.16	88	0.11	2
Cerebrovascular anomalies	431	0.52	20	0.02	2
Hemiplegia	1724	2.08	92	0.11	1
Motor skill disorders	304	0.37	17	0.02	1
Encephalitis (except that caused by TB or STD)	340	0.41	19	0.02	1
Benign neoplasm of cerebral meninges	712	0.86	43	0.05	1
Pervasive developmental disorders	1979	2.38	140	0.17	1
Intrauterine hypoxia and birth asphyxia	72	0.09	5	0.01	1
Intracranial hemorrhage	1237	1.49	92	0.11	1
Respiratory distress syndrome	65	0.08	5	0.01	1
Congenital anomalies of skull and facial bones	150	0.18	13	0.02	1
Aspiration pneumonitis; food/vomitus	952	1.15	85	0.10	1
Spina bifida	215	0.26	20	0.02	1
Congenital hip deformity	211	0.25	20	0.02	1
Occlusion of cerebral arteries	4102	4.94	456	0.55	9
Late effects of cerebrovascular disease	3354	4.04	375	0.45	9
Other dependence on machines	59	0.07	6	0.01	9
Acute but ill-defined cerebrovascular accident	3526	4.25	437	0.53	9

CI= Confidence interval; IHCIS= Integrated Healthcare Information Services

Table 10. Prevalence and odds ratios for the 25 comorbidities with the highest odds ratios comparing cases and controls during or before the analysis period in the IHCIS

Comorbidity	Number Cases	Percent Cases	Number Controls	Percent Control
Convulsions	76929	92.64	58	0.07
Intellectual disabilities	3836	4.62	52	0.06
Microcephalus	818	0.99	12	0.01
Congenital hydrocephalus	780	0.94	17	0.02
Cancer of brain and nervous system	3219	3.88	121	0.15
Developmental disabilities	3129	3.77	153	0.18
Other nervous system congenital anomalies	2545	3.06	119	0.14
Other paralysis	6590	7.94	315	0.38
Hemiplegia	4776	5.75	285	0.34
Cerebrovascular anomalies	1506	1.81	87	0.10
Intracranial hemorrhage	4660	5.61	307	0.37
Learning disorders	4539	5.47	324	0.39
Benign neoplasm of cerebral meninges	1530	1.84	98	0.12
Coma; stupor; and brain damage	20114	24.22	1715	2.07
Encephalitis (except that caused by TB or STD)	1264	1.52	80	0.10
Motor skill disorders	1047	1.26	79	0.10
Pervasive developmental disorders	2978	3.59	251	0.30
Aspiration pneumonitis; food/vomitus	2675	3.22	218	0.26
Occlusion of cerebral arteries	11582	13.95	1286	1.55
Secondary malignancy of brain/spine	619	0.75	52	0.06
Congenital hip dislocation	569	0.69	49	0.06
Mental disorders due to general medical conditions not elsewhere classified	2139	2.58	192	0.23
Dissociative disorders	185	0.22	16	0.02
Acute but ill-defined cerebrovascular accident	9617	11.58	1233	1.48
Late effects of cerebrovascular disease	7766	9.35	967	1.16

Drug	N (%)
Anti-Epileptic Drugs	26584 (97.3)
Anti-depressants	4806 (17.6)
Valproic acid	9293 (34.0)
Carbamazepine	8776 (32.1)
Lamotrigine	5020 (18.4)
Phenytoin	4757 (17.4)
Levetiracetam	2977 (10.9)
Phenobarbital	1645 (6.02)
Clobazam	1161 (4.3)
Topiramate	1133 (4.2)
Gabapentin	784 (2.9)
Clonazepam	733 (2.7)
Primidone	570 (2.1)
Pregabalin	507 (1.9)

GPRD= General Practice Research Database. Note: the following anti-epileptic drugs were prescribed to <1% of the patients with epilepsy: zonisamide, oxcarbazepine, ethosuximide, lacosamide, vigabitrin, acetazolamide, rufinamide, tiagabine hydrochloride, paraldehyde, stiripentol, sultiame or mesuximide. No patients were prescribed beclamide, dipotassium clorazepate, eslicarbazepine acetate, or fosphenytoin sodium.

Table 11. Prevalence of use of anti-convulsants and anti-depressants in epilepsy patients during the one-year period of observation from 01 Jan 2009 to 31 Dec 2009 in GPRD

Drug Category	N (%)
Control of epilepsy	26595 (97.3)
Neuropathic pain	14297 (52.3)
Non-opioid analgesics	10861 (39.7)
Antimanic drugs	8859 (32.4)
Non-steroidal anti-inflammatory drugs	8249 (30.2)
Opioid analgesics	6516 (23.8)
Broad-spectrum penicillins	5763 (21.1)
Statins	5530 (20.2)
Urinary-tract infections	5308 (19.4)
Proton pump inhibitors	5244 (19.2)
Topical corticosteroids	4856 (17.8)
Antiplatelet drugs	4587 (16.8)
Selective beta-2-agonists	3983 (14.6)
Anxiolytics	3684 (13.5)
Emollient skin preparations	3535 (12.9)
Osmotic laxatives	3362 (12.3)
Hypnotics	3345 (12.2)
Angiotensin-converting enzyme inhibitors	3274 (12.0)
Skeletal muscle relaxants	3064 (11.2)
Anxiolytics and neuroleptics (in anaesthesia)	3041 (11.1)
Selective serotonin re-uptake inhibitors	2886 (10.6)
Prophylaxis of migraine	2863 (10.5)
Corticosteroids (inhaled for respiratory conditions)	2859 (10.5)
Beta-adrenoceptor blocking drugs	2819 (10.3)
Drugs used in nausea and vertigo	2747 (10.1)

BNF= British National Formulary; GPRD= General Practice Research Database

Table 12. Prevalence of use of the top 25 most frequent medications in epilepsy patients during the one-year period of observation from 01 Jan 2009 to 31 Dec 2009, by BNF Category in GPRD

Drug	N (%)
Anti-depressants	10378 (22.1)
Anticonvulsants- antiepileptics	35543 (75.8)
Lamotrigine	7157 (15.3)
Phenytoin	6877 (14.7)
Carbamazepine	5549 (11.8)
Topiramate	3976 (8.5)
Clonazepam	2973 (6.3)
Gabapentin	2279 (4.9)
Phenobarbital	2070 (4.4)
Valproate	503 (1.1)
Ethosuximide	428 (0.9)
Methsuximide	16 (0.03)

IHCIS= Integrated Healthcare Information Services

Table 13. Prevalence of use of anti-convulsants and anti-depressants in epilepsy patients during the one-year period of observation from 01 Jan 2009 to 31 Dec 2009 in IHCIS

Drug Category	N (%)
Seizure disorders	34723 (74.0)
Codeine & Comb, Non-Inj	10742 (22.9)
Extended spectrum macroli	8784 (18.7)
Benzodiazepines	7715 (16.5)
SSRI	7037 (15.0)
HMG-COA reductase inhibitors	6693 (14.3)
Aminopenicillins	6304 (13.4)
Hormones, Cort plain, oral	5941 (12.7)
Cephalosporins & related	5829 (12.4)
Proton pump inhibitors	5642 (12.0)
Anti-arthritis, plain	5627 (12.0)
Quinolones, systemic	5525 (11.8)
Beta blockers	4332 (9.2)
Steroid, inhaled nasal	4244 (9.1)
B-lactam, increased activity	4212 (9.0)
Mus relx, non-surg,W/O ANA	4150 (8.9)
Hormones,Cort plain, derm	3732 (8.0)
Thyroid hormone, synth	3616 (7.7)
ACE Inhib, alone	3579 (7.6)
Beta agonists, aerosol	3522 (7.5)
Antivirals, other	3482 (7.4)
Sulfa & Trimeth comb	3020 (6.4)
Calcium blockers	2690 (5.7)
Antipsychotics, other	2638 (5.6)
Analeptics	2493 (5.3)

Table 14. Prevalence of use of the top 25 most frequent medications in epilepsy patients during the one-year period of observation from 01 Jan 2009 to 31 Dec 2009, by Universal System Classification Fourth Level in IHCIS

4. Discussion

Electronic medical record systems provide an opportunity to identify treatment patterns and comorbidities in a large diagnosed disease population. They also allow for comparisons between the relative prevalence estimates of various comorbidities within the same data source. The comorbidities were ranked by how prevalent they were in epilepsy cases, and then by the ORs comparing cases to controls. The conditions with the highest ORs have the strongest associations with epilepsy compared to matched controls, therefore these findings may be hypothesis-generating for conditions related to epilepsy, though temporality cannot be established in this cross-sectional study. For instance, these can be tested as risk factors for epilepsy; conversely, epilepsy can be examined as a risk factor for these associated conditions.

The definition of both cases and controls requires that patients are registered throughout the full lead-in and analysis periods. The lead-in period is used to identify existing epilepsy patients to ensure that all cases have epilepsy prior to the start of the observation period. This ensures that patients are "at risk" of receiving management for epilepsy throughout the observation period when the patient's status is being assessed. This cross sectional approach, based on a set calendar index date, means there is no restriction of the duration of epilepsy prior to the start of observation, and the population is likely to contain both prevalent and newly-diagnosed epilepsy cases. The use of an index date tied to an individual patient (such as their first diagnosis on a database) is another possible approach, which is more tailored incident cases (or patients at an earlier stage of the disease) and historical rather than recent management patterns.

Diagnosed prevalence rates were similar in a US insurance claims database (0.5%) and a UK general practice-based electronic medical record system (0.8%), although peak age prevalence differed, likely based on the patient populations covered by these systems. The IHCIS system under-represents the elderly population, because it mainly consists of the employed, insured population. These prevalence estimates are similar to those reported in the literature for studies with records-based methodology, ranging from 3 to 8 per 1000 persons (Banerjee et al., 2009).

Many diagnosed comorbidities, including psychiatric and neurological comorbidities, were more prevalent in the patients with epilepsy compared to matched controls. A previous study in the GPRD also reported that many conditions were associated with epilepsy (Gaitatzis, 2004). The current study supports the evidence that the burden of epilepsy along with its comorbidities is high compared to the general population.

Major depression is a common co-morbidity of epilepsy with at least 20% of epilepsy patients experiencing mild to severe depressive symptoms (O'Donoghue et al., 1999; Mendez et al., 1986; Hermann et al., 1986; Baker et al., 1996; Cramer et al., 2004; Jacoby et al., 1996; Boylan et al., 2004; Beghi et al., 2002). In the current study, 29% of patients with epilepsy in the GPRD (OR= 1.5, 95%CI: 1.4-1.5), and 24% of patients with epilepsy in the IHCIS (OR=2.6, 95%CI: 2.5-2.7) had a diagnosis of depression in the analysis period or before. Studies using structured psychiatric interviews in epilepsy clinics, likely to represent more severe epilepsy patients, have reported a prevalence of major depression of up to 55% (Mendez et al., 1996). However, the cross-sectional nature of most studies prevents inferences concerning the temporal order of disease development. When

longitudinal analyses have been completed a history of major depression has been associated with an increased risk for incident epilepsy and first unprovoked seizure (Nilsson et al., 2003; Forsgren & Nystrom 1990; Hesdorffer et al., 2006; Hesdorffer et al., 2000).

Certain epilepsy types may be at increased risk of depression: the mean estimated lifetime prevalence of depression is 30% for patients with temporal lobe epilepsy and refractory epilepsy with corresponding risks in the general population of between 6% and 17% (Glosser et al., 2000). Studies have consistently identified co-morbid depression as a powerful predictor of poor health related quality of life in epilepsy patients even after adjustment for seizure frequency and severity (Kanner, 2009). Depression is also a strong predictor for increased suicidality among epilepsy patients (Kanner, 2009).

The prevalence of anxiety disorders is consistently higher (approximately twofold increased risk) among epilepsy patients than the general population. In the current study, 21% of patients with epilepsy in the GPRD (OR= 1.4, 95%CI: 1.3-1.5), and 26% of patients with epilepsy in the IHCIS (OR=2.1, 95%CI: 2.1-2.2) had a diagnosis of anxiety in the analysis period or before. Studies using a range of disease measurement scales, and capturing patients mainly through cross sectional health surveys, have reported point prevalence estimates in epilepsy patients of 11% to 39% (Gaitatzis et al., 2004; Tellez-Zenteno et al., 2007; Edeh & Toone, 1987; Stirne et al., 2005; Kobau et al., 2006). The variation is likely to reflect the selection of different subsets of the epilepsy population with higher prevalence estimates observed among patients with temporal lobe epilepsy.

The prevalence of psychoses in epilepsy, as reported from population-based studies, ranges from 2% to 7% (Gaitatzis et al., 2004). The prevalence varies by epilepsy type with estimates of 10% to 19% reported among individuals with temporal lobe epilepsy, nearly double the risk associated with generalised epilepsy, though larger differences have been reported in older studies (Gaitatzis et al., 2004; Shukla et al., 1979). Gender differences have also been reported with females at an increased risk of psychoses. An Icelandic study reported 6% prevalence in males with epilepsy versus 9% in females (Gudmundsson, 1966). In the current study, 9% of patients with epilepsy in the IHCIS (OR=9.7, 95%CI: 9.0-10.4) had a diagnosis of psychosis in the analysis period or before.

The incidence of psychoses is reported to be 3 to 12 times higher in epilepsy patients than the general population. The range again depends on the epilepsy population sampled (seizure type and severity) as well as the instrument used to diagnose psychosis (Bredkjaer et al., 1998; Torta & Keller, 1999). Patients undergoing epilepsy surgery are at particular risk of developing psychoses for the first time. Interictal psychoses can develop in 3% to 12% of patients following anterior temporal lobectomy and seizure-related psychoses can affect 1% to 13% of patients (Gaitatzis et al., 2004; Gaitatzis et al., 2004 (2)).

Studies concentrating solely on schizophrenia have reported prevalence estimates of 4% to 18% among patients with epilepsy (the majority suffering from temporal lobe epilepsy) (Gaitatzis et al., 2004; Gaitatzis et al., 2004 (2)). The expected prevalence of schizophrenia in the general population is 1% (Toone, 2000). Patients with schizophrenia are also at an increased risk of seizures related to the condition itself and to exposure to psychotropic medications that lower seizure threshold (e.g. clozapine) (Torta & Keller, 1999). In the current study, 1% of patients with epilepsy in the GPRD (OR=2.8, 95%CI: 2.5-3.1) had a diagnosis of schizophrenia in the analysis period or before.

Suicide is a much discussed cause of death in epilepsy patients, especially with the recent analysis by the US Food and Drug Administration in 2008 that showed an association between AEDs and suicidality in pooled clinical trials. Population-based studies report that between 0% and 9% (Sweden and Iceland, respectively) of deaths among patients with epilepsy result from suicide (Tomson et al., 2004). However it is not clear whether epilepsy or its treatment increases the risk of suicide: suicide attempt has been associated with an increased risk for developing epilepsy indicating the association could represent the recurrence, post epilepsy diagnosis, of an underlying suicidality risk 74. The GPRD and IHCIS results indicate an association between epilepsy diagnosis and suicidality, with an OR of 2.8 (95% CI: 2.5-3.1) in GPRD and 5.5 (95% CI: 5.2-6.0) in IHCIS for during or ever before the analysis period.

The reported prevalence of migraine among epilepsy patients ranges from 8% to 23% (Marks & Ehrenberg, 1993) compared with 12% in the general population (Lipton et al., 2007). While the majority of studies report the risk of migraine to be two-fold greater among epilepsy patients (Lipton et al., 1994), two studies failed to confirm this association (Karaali-Savrun et al., 2002; Nuyen et al., 2006). This discordance is most likely due to differences in migraine definition and the absence of well defined control groups in some studies. Recent studies indicate that the association is primarily with migraine with aura, though the absolute prevalence of migraine with aura among epilepsy patients has yet to be reported (Piccinelli et al., 2006).

The IHCIS and GPRD database studies supported a positive association between epilepsy and migraine. A history of diagnosed migraine was present in 16% of epilepsy cases and 5% of controls in the IHCIS database study (OR = 3.7, 95% CI: 3.6-3.8). In the GPRD database, 9% of cases and 7% of controls had a history of diagnosed migraine (OR= 1.3, 95% CI: 1.3-1.4). The differential prevalences between the databases likely reflect between-country differences in diagnostics, awareness and treatment of migraine.

The current medication data was only reported for the patients with epilepsy to determine the most commonly used medications among patients with epilepsy. The most common AEDs varied between the US and UK databases. This is likely due to different treatment patterns and guidelines in the two countries. It has previously been shown that there is an association between the first AED prescribed after diagnosis of and history of psychiatric disorders, including depression and bipolar disorder, and the differential prescribing varied between the US and UK (Ishihara et al., 2010). One potential use of these data is to characterise polypharmacy patterns to inform potential drug interaction studies. Since the majority of patients are prescribed AEDs, the list identifies other medication types that are commonly used among the epilepsy patients.

The study should be interpreted in the context of its strengths and potential limitations. The strengths of the study include the large sizes of the databases, and the availability of detailed diagnosis and medication records. The GPRD is representative of the general population of the UK, and the IHCIS is representative of the US insured population. The IHCIS database is a large sample of people in the US covered by private insurance plans. Therefore results of this study may not be representative of US patients who receive healthcare through government organizations (e.g., Medicare, Medicaid) or who lack health insurance; for instance, these patients may be more likely to receive generic or older AEDs. In both databases, only diagnosed diseases are recorded, and therefore patients had to

present to healthcare to be diagnosed with conditions or prescribed medications. There is a possibility of confounding by consultation frequency because patients with epilepsy or other chronic medical conditions will be more likely to be seen by healthcare providers compared to the general population.

The results of this study can be used to generate hypotheses about which medical conditions may be associated with epilepsy (either as risk factors for epilepsy, or resulting from epilepsy). Understanding the comorbidities and medication patterns in epilepsy also informs the effects of eligibility criteria on clinical trial recruitment, and facilitates assessments of potential safety signals that may arise in clinical trials (e.g. if a conditions is more common within the disease population at baseline, then this should be taken into account in evaluating whether exposure to a medication is associated with that condition).

5. Conclusion

In conclusion, psychiatric, neurological and other comorbidities are more common in patients with epilepsy, compared to age-, sex-matched controls. The results of this study provide hypotheses about conditions which may be associated with epilepsy, and these may be the subject for further investigation.

Among patients with epilepsy, the most commonly prescribed medications varied between the UK and US. Two of the older AEDs, valproate and carbamazepine, were the most commonly prescribed AEDs in 2009 amongst epilepsy patients in GPRD. Lamotrigine and phenytoin were the most commonly prescribed AEDs to patients with epilepsy in 2009 within IHCIS.

The most commonly prescribed medications among the epilepsy patient population, aside from AEDs, included analgesics, non-steroidal anti-inflammatory drugs, extended spectrum macroli (anti-biotics), selective serotonin reuptake inhibitors, and statins. The list of commonly prescribed medications in the epilepsy patient population can give an indication as to which drugs to consider for possible drug-drug interactions.

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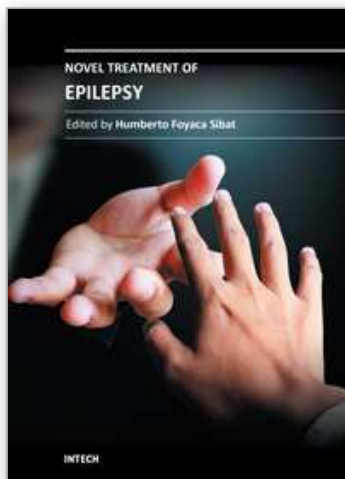
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Epilepsy continues to be a major health problem throughout the planet, affecting millions of people, mainly in developing countries where parasitic zoonoses are more common and cysticercosis, as a leading cause, is endemic. There is epidemiological evidence for an increasing prevalence of epilepsy throughout the world, and evidence of increasing morbidity and mortality in many countries as a consequence of higher incidence of infectious diseases, head injury and stroke. We decided to edit this book because we identified another way to approach this problem, covering aspects of the treatment of epilepsy based on the most recent technological results â€œin vitroâ€ from developed countries, and the basic treatment of epilepsy at the primary care level in rural areas of South Africa. Therefore, apart from the classic issues that cannot be missing in any book about epilepsy, we introduced novel aspects related with epilepsy and neurocysticercosis, as a leading cause of epilepsy in developing countries. Many experts from the field of epilepsy worked hard on this publication to provide valuable updated information about the treatment of epilepsy and other related problems.

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