Postprint Version	1.0
Journal website	http://onlinelibrary.wiley.com/doi/10.1111/epi.12557/abstract
Pubmed link	http://www.ncbi.nlm.nih.gov/pubmed/24575970
DOI	10.1111/epi.12557

Antiepileptic drug use in seven electronic health record databases in Europe: A methodologic comparison

MARK C. H. DE GROOT, MARKUS SCHUERCH, FRANK DE VRIES, ULRIK HESSE, BELÉN OLIVA, MIGUEL GIL, CONSUELO HUERTA, GEMA REQUENA, FRANCISCO DE ABAJO, ANA S. AFONSO, PATRICK C. SOUVEREIN, YOLANDA ALVAREZ, JIM SLATTERY, MARIETTA ROTTENKOLBER, SVEN SCHMIEDL, LISET VAN DIJK, RAYMOND G. SCHLIENGER, ROBERT REYNOLDS, OLAF H. KLUNGEL

SUMMARY

Objective: The annual prevalence of antiepileptic drug (AED) prescribing reported in the literature differs considerably among European countries due to use of different type of data sources, time periods, population distribution, and methodologic differences. This study aimed to measure prevalence of AED prescribing across seven European routine health care databases in Spain, Denmark, The Netherlands, the United Kingdom, and Germany using a standardized methodology and to investigate sources of variation.

Methods: Analyses on the annual prevalence of AEDs were stratified by sex, age, and AED. Overall prevalences were standardized to the European 2008 reference population.

Results: Prevalence of any AED varied from 88 per 10,000 persons (The Netherlands) to 144 per 10,000 in Spain and Denmark in 2001. In all databases, prevalence increased linearly: from 6% in Denmark to 15% in Spain each year since 2001. This increase could be attributed entirely to an increase in "new," recently marketed AEDs while prevalence of AEDs that have been available since the mid-1990s, hardly changed. AED use increased with age for both female and male patients up to the ages of 80 to 89 years old and tended to be somewhat higher in female than in male patients between the ages of 40 and 70. No differences between databases in the number of AEDs used simultaneously by a patient were found.

Significance: We showed that during the study period of 2001–2009, AED prescribing increased in five European Union (EU) countries and that this

increase was due entirely to the newer AEDs marketed since the 1990s. Using a standardized methodology, we showed consistent trends across databases and countries over time. Differences in age and sex distribution explained only part of the variation between countries. Therefore, remaining variation in AED use must originate from other differences in national health care systems.

Antiepileptic drugs (AEDs) are widely prescribed in Europe. Up to 1.1% of the population is estimated to use AEDs, and their use is increasing yearly.[1, 2] AEDs are a heterogeneous pharmacologic class with respect to chemical structure, postulated mechanisms of action, and indications.[3] Although the main therapeutic indication includes epilepsy, these drugs are also widely and increasingly prescribed for bipolar disorder, depression, neuralgia, migraine, and neuropathic pain.[4] The newer compounds that became available since the mid-1990s—such as gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazapine, pregabalin, topiramate, and zonisamide—are registered and used for an even broader spectrum of psychotropic indications.[5] Several adverse drug reactions on the central nervous system (CNS) have been associated with AED use, presumably related to AEDs passing through the blood–brain barrier.[6] Estimation of safety and absolute risks requires reliable figures on drug use in populations. Although there has been an increase in electronic health care datasets that can be used for drug safety surveillance and pharmacoepidemiologic studies, it is challenging to derive consistent results on both drug exposure and outcomes due to large heterogeneity in methods, data sources, terminology, and countries.[1, 7] This study is performed within the framework of PROTECT (Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium).[8, 9] The aim of these studies in work package 2 is to develop, test, and disseminate methodologic standards for the design, conduct, and analysis of pharmacoepidemiologic studies applicable to different safety issues and using different data sources. To achieve this we explore in this study the exposure to AEDs on a population level as recorded in seven different data sources in five different Western European countries using the same methodology.

METHODS

Data sources

We analyzed data from the following databases, all using a common research protocol and data specification: (1) The "Base de datos Informatizada para estudios Farmacoepidemiologicos en Atencion Primaria" (BIFAP)—A Spanish database of medical records of primary care; (2) The Danish Register of medicinal product statistics (Danish Registries); (3) The Mondriaan Netherlands Primary Care Research Database (NPCRD); (4) The Dutch Mondriaan Almere Health Care group (AHC) database, (5) The Health Improvement Network (THIN from the United Kingdom); (6) The UK Clinical Practice Research Datalink (CPRD; formerly known as General Practice Research Database [GPRD]); and (7) Database of the National Association of Statutory Health Insurance Physicians of Bavaria ("Kassenärztliche Vereinigung Bayerns"), henceforth referred to as the Bavarian Claims Database (KVB).

We describe the seven databases below and present additional information in Table 1.

[TABLE 1]

BIFAP is a nonprofit research project, kept by the Spanish Agency for Medicines and Medical Devices (AEMPS), a public agency belonging to the Spanish Department of Health. The project started in 2003, including information from 2001 onwards. The database contains coded and anonymous data from general practitioners (GPs) and pediatricians on patient demographics, prescription details, clinical events, specialist referrals, and laboratory test results, from around 3.2 million patients covering approximately 6.8% of the Spanish population.[10]

The Danish Register of Medicinal Product Statistics, currently maintained by the Statens Serum Institut (SSI), contains information on all medication dispensing on a pharmacy level and is linked via the Danish Civil Registration System[11] to individuals who redeemed the prescription from 1994 onwards, causes of death for the entire population (5.3 million inhabitants), and contact information of visits to GPs as well as specialists in private care.[12]

The Dutch Mondriaan project is a private-public collaboration funded by the Dutch TOP institute Pharma (www.tipharma.com). Health care data from various sources are pseudonymized and anonymized, linked, and disclosed for research.[13] The cumulative number of persons having data in Mondriaan reaches around 1.4 million comprising mainly GP data complemented by pharmacy dispensing data and linkages to survey data. For this study, data from two GP databases were used. The Mondriaan-NPCRD comprised a network of 84 GP practices all over the Netherlands, with >700,000 registered patients and is coordinated by NIVEL, The Netherlands Institute for Health Services Research.[14] The Mondriaan-AHC started in the early 1990s and holds the medical GP and pharmacy records and laboratory values of >260,000 inhabitants of the young and fast growing city of Almere. Both databases hold longitudinal data on patient contacts, including diagnoses, referrals, and prescriptions, and cover 3.7% of the Dutch population.

The two United Kingdom general practice databases, THIN and CPRD, collect and archive the electronic medical records of >3 and >5 million active patients, respectively, covering >8% of the United Kingdom population. The United Kingdom databases overlap to some extent, but in 2012 they provided unique information for 268 and 168 practices, respectively.[15-17]

Data from the Bavarian Claims Database are extracted from the Bavarian Association of Statutory Health Insurance Physicians accounting system.[18] The German database includes population-based data on diagnoses and medical services and covers around 10.5 million people (84% of the Bavarian population) linked to outpatient treatment data through GPs and specialists.[18] Records contain no specific dates but only information on the quarter of the year a prescription was issued or a diagnosis was made.

Study population and period of valid data collection

Patients in the databases having an active registration status during the study period, which lasted from January 1, 2001 to December 31, 2009, were eligible for inclusion. Valid data collection started at the date when a practice became up to research

quality standard (if applicable), the date when a patient enrolled into a practice, or the date that a practice was enrolled into the database, whichever came last. The follow-up time of patients was censored on the date a patient died; the date a patient was transferred out of the practice; the end of the database's data collection, or the date that the practice left the database, whichever came first.

In the Mondriaan-AHC, the last available year of data collection was 2008. The KVB provided data from 2004 until 2008.

Exposure definition

We considered in this study AEDs with approved indications for epilepsy and seizures in all the five countries. Fourteen AED medications were identified, which were analyzed individually, and five AED medications not available with an approved AED indication in *every* country were grouped into "other AEDs." AEDs available on the market before 1990 were classified as "old" AEDs and those marketed after 1995 were classified as "new" AEDs.[1, 19] The list of these drugs is included in Table 2. Because the United Kingdom uses the British National Formulary (BNF) to code drug use, the Anatomical Therapeutic Chemical (ATC) classification system codes were translated into BNF codes based on the active ingredient.

[TABLE 2]

Calculation of period prevalence and standardization to reference population

The period prevalence per year was calculated by dividing the number of patients having received at least one prescription for any AED defined earlier by the number of people present in every database at mid-year. To prevent biases due to irregularities caused by the holiday season, mid-year was defined as June 1. We calculated crude and age (10-year bands) and sex-stratified prevalences. To take into account different age and sex distributions of the source populations, a standardized overall prevalence was computed by direct standardization weighting all the strata according to the age and sex distribution in the 2008 European population.[20] Annual prevalences versus calendar year were fitted in each database over the whole study period using linear regression.

Concomitant drug use

To distinguish between monotherapy and combined therapy with multiple AEDs, point prevalences were computed by counting for each patient the number of AED prescriptions covering June 1 and stratified into categories (1, 2, 3, 4, and 5+). Durations of prescriptions were extracted from the prescriptions. In Mondriaan-AHC and -NPCRD, durations were imputed to 90 days if missing because that is the modal duration for prescriptions of chronic medication in The Netherlands.

RESULTS

Overall prevalence of prescribed AEDs

Figure 1 shows crude prevalences (A) and prevalences standardized for age and sex distribution (B). In 2001 the standardized overall period prevalence was lowest in the Dutch databases Mondriaan-NPCRD and Mondriaan-AHC, with 88 and 109 prescriptions, respectively, per 10,000 persons. In 2001 the standardized overall period prevalence was highest in the Spanish BIFAP, the Danish Registries, and THIN in the United Kingdom databases, with 144 and 145 prescriptions, respectively, per 10,000 persons. CPRD, the other United Kingdom database, had a lower period prevalence of 114 in 2001. The difference between CPRD and THIN remained constant over the study period. The KVB lines up very tightly with THIN and Mondriaan-AHC from 2004 to 2008, the period for which KVB has data available. All databases show an increase of AED prevalence during the study period that is linear ($r^2 > 0.913$ in all databases). This yearly increase in overall period prevalence ranges from 5.8% in Danish Registries, 7.5% in THIN, 8.1% in Mondriaan-NPCRD, 8.7% in Mondriaan-AHC, 9.6% in CPRD, to 14.9% in BIFAP compared to the original prevalence in 2001. In KVB this increase was 8.1% per year from 2004 onward.

[FIGURE 1]

In a sensitivity analysis in the Mondriaan-AHC database, 30% of all AED prescriptions was issued by specialist (non-GP) doctors.

Comparison by age and sex

The mean age of persons that received at least one AED prescription in a year was on average 50.5 ± 2.0 years (mean ± standard deviation [SD]) in 2001 in all databases and gradually increased to 54.0 ± 1.2 years in 2008. The AED users in Denmark and Mondriaan-AHC were somewhat younger, respectively, 2.0 and 4.6 years on average, than users in other databases during the whole study period. KVB had the oldest AED users, who were on average 4.0 years older.

In all databases the prevalence of AED prescribing increased many-fold with higher age categories to a maximum AED prevalence in the age group of 80–89 years (as high as 679 per 10,000 females in BIFAP in 2008). In all databases AED prevalence in females was higher than for males, and this difference ranged from 16% in KVB to 37% higher prevalence in BIFAP in 2008. Figure 2 shows assessment of this sex difference over age categories in 2008. The difference between females and males is present between age categories 40–49 up to 70–79 years. In KVB the prevalence of AED use in male and female AED users remained almost equal over life course.

[FIGURE 2]

Individual AEDs: old and new AEDs

In the analysis of prevalence of individual AEDs in Figure 3 it is clear that the increase of prevalence differs considerably between AEDs. In addition, the prescription of "old" AEDs (plotted at the bottom ends of the bars in Fig. 3) tends to remain stable or decreases slightly over time in all databases. The newer AEDs, and gabapentin, pregabalin, lamotrigine, levetiracetam, and topiramate in particular, are

responsible for the increase of AED prevalence over time. Prevalences of AEDs in the other AED group were stable over the study period.

[FIGURE 3]

Concomitant AED prescription

The number of different AED medications a patient was prescribed simultaneously or concomitantly is quite similar in all databases. Most patients were prescribed monotherapy 87 ± 2% (mean ± SD), followed by 12 ± 1% having two and only 2.1 ± 0.6% with more than two AEDs concomitantly in all countries.

DISCUSSION

In this study we compared the prevalence of prescription of drugs licensed for treatment of epilepsy using six electronic healthcare databases and one claims database in five Western European countries using a standardized methodology. During the whole 9-year study period we observed a continuous and steady increase of the prevalence of AED prescribing; however, many of the newer drugs indicated for epilepsy have other indications or off-label uses, and this may explain the increase.

Overall prevalence of AED use

After standardization by age and sex, we observed a linear increase in the prevalence of AED use of 6–9% per year from 2001 onward in Denmark, The Netherlands, the United Kingdom, and Germany. In Spain the yearly increase is even higher (14.9%). Our results are in line with observations from a Norwegian study by Johannessen Landmark et al.[21] using a drug dispensing database in which they found a somewhat steeper increase in AED *dispensing* prevalence from 122 per 10,000 in 2004 up to 208 per 10,000 in 2007, which corresponds to 17.6% per year. A cross-sectional prescription study revealed a prevalence of 250 per 10,000 in Germany in 2009.[1] Precise comparisons of overall prevalence rates of AED prescription in these studies is difficult, as both studies differ from our study with respect to database type, population distribution in Norway, and the use of a different definition of AEDs in the German study. The small decrease in variation between databases after standardization to a reference population showed that only part of the variance in this study is caused by differences in sex and age distribution between populations.

Individual AEDs, old and new

Until the early 1990s there were six major compounds on the market categorized as antiepileptic drugs and these are often referred to as "old" AEDs.[19, 22] The newer compounds that became available since then are called "new" AEDs. The increase in overall prevalence we observed in the whole study period is entirely attributable to an increase of prescription of "new" AEDs. This is also seen in recent studies in Germany, Norway, Italy, and Denmark.[1, 21-23] Subanalyses within these studies have proposed that use of newer AEDs increases because these substances would

have other indications in addition to epilepsy.[23] Hamer et al.[1] were able to use a disease register to verify the epilepsy status of patients and observed that only 36% of their AED users in Germany had epilepsy. This is supported by the observation by Savica, showing that for new AEDs the indication of use in epilepsy dropped from 43% to 17% in Italy between 2000 and 2005.[22]

Age and sex

This study showed an increase in AED use in higher age groups up to ages of 80–89 years old. A similar course over age is reported by Johannessen Landmark et al.,[24] while assessing AED prescribing for the indication of epilepsy. A decrease at the highest age category 90+ is consistent with other observations[24, 25] and might be explained by cautious prescribing in the very elderly and a "healthy survivor effect."[26] The slightly higher prevalence in AED use in female patients we observed was also seen by Tsiropoulos et al.[23] in Denmark, who attributed this entirely to the use of the new AEDs. Oteri et al.[27] observed a higher and preferential use of new AEDs in elderly females over 65 years, whereas in a combined study in Italy, The Netherlands, and the United Kingdom, in GP databases pediatric AED use remained stable and low until at least 2005.[28]

Concomitant AED use

Our observation that 86% of AED users receive monotherapy is similar to patients with epilepsy in Norway where 82% were using a single therapy in 2007.[24] Hamer et al.[1] found 68% of patients in Germany were using monotherapy in 2009, although they used a broader AED list including benzodiazepines.

Prescription versus dispensing data

Six of the databases in this study are primary care data sources, suggesting that medication issued by other doctors in hospitals, by specialist doctors, or private clinics may not have been captured in the primary care record. We assume that part of the refills of prescriptions issued initially by neurologists, psychiatrists, or specialist doctors are likely to be included in the datasets from Spain, the United Kingdom, and The Netherlands. In these countries, refills of prescriptions originating with a specialist are often handled in primary care and dispensed at the local pharmacy. In this study we see a continuous difference over time in standardized overall prevalence between the Dutch Mondriaan-NPCRD and the Mondriaan-AHC, as the latter includes also dispensing records from local pharmacies. An interesting observation is that 30% of the dispensed AED prescriptions in the Mondriaan-AHC database originated from specialist (non-GP) doctors, which equals the difference in prevalence compared to the other Dutch database Mondriaan-NPCRD having only prescriptions from GPs.
In Denmark, medicines given to a patient at a hospital are not covered in the registry. The Bavarian Claims database has claims of all AED prescriptions in outpatients.
A limitation of this study is that we were not able to reliably estimate indications of AED use as, depending on the database, in 47–95% of the patients the indication could not be estimated at all. This was because either direct links between prescriptions and indications were lacking or incomplete or assignment of indications for AEDs was not reliable due to the broad spectrum of indications associated with

this drug class and patients having more than one suitable indication in their medical history. We do not think that this will heavily impact the value of these databases for future observational studies because medical outcomes and comorbidities are well documented in all databases and can be used to adjust for potential confounding in observational association studies.

In summary ,this study shows a consistent increase in AED use in five European countries using standardized methodology in routine health care data from primary care, a whole population registry, and claims data. An increasing prevalence of prescription of newer AEDs, far more than the number of patients diagnosed with epilepsy,[29] indicates that more people seem to use AEDs for indications other than epilepsy. Differences in age and sex distribution explained part of the variation between countries. The number of AEDs a patient uses concomitantly is similar in all databases. Finally, routine health care data from electronic primary care–based sources enable pharmacoepidemiologic studies in—or representative of—large proportions of the population to shed light for drug safety in AED use.[7]

REFERENCE

1 Hamer HM, Dodel R, Strzelczyk A, et al. Prevalence, utilization, and costs of antiepileptic drugs for epilepsy in Germany – a nationwide population-based study in children and adults. J Neurol 2012;259:2376–2384.

2 Alacqua M, Trifiro G, Spina E, et al. Newer and older antiepileptic drug use in Southern Italy: a population-based study during the years 2003–2005. Epilepsy Res 2009;85:107–113.

3 Perucca E. An introduction to antiepileptic drugs. Epilepsia 2005;46(Suppl. 4):31–37.

4 Ettinger AB, Argoff CE. Use of antiepileptic drugs for nonepileptic conditions: psychiatric disorders and chronic pain. Neurotherapeutics 2007;4:75–83.

5 Perucca E, Tomson T. The pharmacological treatment of epilepsy in adults. Lancet Neurol 2011;10:446–456.

6 Johannessen Landmark C. Antiepileptic drugs in non-epilepsy disorders: relations between mechanisms of action and clinical efficacy. CNS Drugs 2008;22:27–47.

7 Landmark CJ, Johannessen SI. Safety aspects of antiepileptic drugs–focus on pharmacovigilance. Pharmacoepidemiol Drug Saf 2012;21:11–20.

8 The pharmacoepidemiological research on outcomes of therapeutics by a European Consortium (PROTECT) objectives of PROTECT. Available at:http://www.imi-protect.eu/objectives.shtml. Accessed September 10, 2012.

9 Abbing-Karahagopian V, Kurz X, de Vries F, et al. Bridging differences in outcomes of pharmacoepidemiological studies: design and first results of the PROTECT project. Curr Clin Pharmacol 2013 Nov 11 [Epub ahead of print].

10 Base de datos para la Investigación Farmacoepidemiolóogicos en Atencion Primaria (BIFAP). A computerized database of medical records of primary care in Spain. Available at:http://www.bifap.org/summary.php. Accessed September 10, 2012.

11 Pedersen CB. The Danish civil registration system. Scand J Public Health 2011;39:22–25.

12 Wallach Kildemoes H, Toft Sørensen H, Hallas J. The Danish national prescription registry. Scand J Public Health 2011;39:38–41.

13 Project Mondriaan. Available at:http://www.projectmondriaan.nl. Accessed September 12, 2012.

14 Stirbu-Wagner I, Dorsman SA, Visscher S, et al. Landelijk Informatienetwerk Huisartsenzorg. Feiten en cijfers over huisartsenzorg in Nederland. Available at:http://www.nivel.nl/representativiteit-van-linh. Accessed September 12, 2012.

15 Clinical Practice Research Datalink (CPRD). Available at:http://www.cprd.co.uk/intro.asp. Accessed September XX, 2012.

16 The Health Improvement Network (THIN). Available at:http://www.thin-uk.com/. Accessed September XX, 2012.

17 Cai B, Xu W, Bortnichak E, et al. An algorithm to identify medical practices common to both the General Practice Research Database and The Health Improvement Network database. Pharmacoepidemiol Drug Saf 2012;21:770–774.

18 KVB The Bavarian Association of Statutory Health Insurance Physicians. Available at:http://www.kvb.de/ueber-uns/. Accessed September 12, 2012.

19 Beghi E. Efficacy and tolerability of the new antiepileptic drugs: comparison of two recent guidelines. Lancet Neurol 2004;3:618–621.

20 European Commission E Database: Population on 1 January 2008 by five years age groups and sex. Available at:http://epp.eurostat.ec.europa.eu/portal/page/portal/statistics/search_database. Accessed November 6, 2012.

21 Johannessen Landmark C, Larsson PG, Rytter E, et al. Antiepileptic drugs in epilepsy and other disorders – a population-based study of prescriptions. Epilepsy Res 2009;87:31–39.

22 Savica R, Beghi E, Mazzaglia G, et al. Prescribing patterns of antiepileptic drugs in Italy: a nationwide population-based study in the years 2000–2005. Eur J Neurol 2007;14:1317–1321.

23 Tsiropoulos I, Gichangi A, Andersen M, et al. Trends in utilization of antiepileptic drugs in Denmark. Acta Neurol Scand 2006;113:405–411.

24 Johannessen Landmark C, Fossmark H, Larsson PG, et al. Prescription patterns of antiepileptic drugs in patients with epilepsy in a nation-wide population. Epilepsy Res 2011;95:51–59.

25 Johnell K, Fastbom J. Antiepileptic drug use in community-dwelling and institutionalized elderly: a nationwide study of over 1,300,000 older people. Eur J Clin Pharmacol 2011;67:1069–1075.

26 Baillargeon J, Wilkinson GS. Characteristics of the healthy survivor effect among male and female Hanford workers. Am J Ind Med 1999;35:343–347.

27 Oteri A, Trifiro G, Gagliostro MS, et al. Prescribing pattern of anti-epileptic drugs in an Italian setting of elderly outpatients: a population-based study during 2004–07. Br J Clin Pharmacol 2010;70:514–522.

28 Hsia Y, Neubert A, Sturkenboom MCJM, et al. Comparison of antiepileptic drug prescribing in children in three European countries. Epilepsia 2010;51:789–796.

29 Ngugi AK, Bottomley C, Kleinschmidt I, et al. Estimation of the burden of active and life-time epilepsy: a meta-analytic approach. Epilepsia 2010;51:883–890.

TABLES AND FIGURES

Table 1. Additional characteristics of the health care databases used in this study

Database	Country	Cumulative population (2008)	Active population (2008)	Data available since	Data source	Coding diagnoses	Coding drugs	Recording of drug use
BIFAP	Spain	3.2 M	1.6 M	2001	GP	ICPC	ATC	Prescribing
The Danish Registries	Denmark	5.2 M	5.2 M	1994 (medical product)	GP + specialist doctors	ICD-10	ATC	Prescribing + dispensing
CPRD	United Kingdom	11.0 M	5.1 M	1987	GP	READ	BNF	Prescribing
THIN	United Kingdom	8.7 M	3.4 M	2003	GP	READ	BNF	Prescribing
Mondriaan								
NPCRD	The Netherlands	1.0 M	0.34 M	1991	GP	ICPC	ATC	Prescribing
AHC		0.26 M	0.17 M	1991	GP/pharmacy	ICPC	ATC	Prescribing + dispensing
Bavarian claims database KVB	Germany	10.5 M	9.5 M	2004	Claims health insurance	ICD-10	ATC	Claims

M, million persons; GP, general practitioners; ICPC, international classification of primary care; READ, Coded thesaurus of clinical terms maintained by the UK National Health service; ICD-9/ICD-10, International Classification of Diseases revision 9 or 10; ATC, The Anatomical Therapeutic Chemical (ATC) classification system; BNF, British National Formulary drug codes used in the United Kingdom.

Table 2. List of AEDs considered in this study		
Drug substance	ATC	Type[a]
Substances individually assessed		
Phenobarbital	N03AA02	Old
Primidone	N03AA03	Old
Phenytoin	N03AB02	Old
Ethosuximide	N03AD01	Old
Carbamazepine	N03AF01	Old
Valproate/valproic acid/sodium valproate	N03AG01	Old
Oxcarbazepine	N03AF02	New
Lamotrigine	N03AX09	New
Topiramate	N03AX11	New
Gabapentin	N03AX12	New
Levetiracetam	N03AX14	New
Zonisamide	N03AX15	New
Pregabalin	N03AX16	New
Lacosamide	N03AX18	New
Substances assessed as "other AEDs" group		
Clobazam	N05BA09	Old
Vigabatrin	N03AG04	New
Tiagabine	N03AG06	New
Rufinamide	N03AF03	New
Stiripentol	N03AX17	New

[a]AEDs available before the mid-1990s are often considered as "old" AEDs.

Figure 1: Annual prevalence of having any AED prescription in all countries, crude (A) and standardized to the European standard reference population (B).
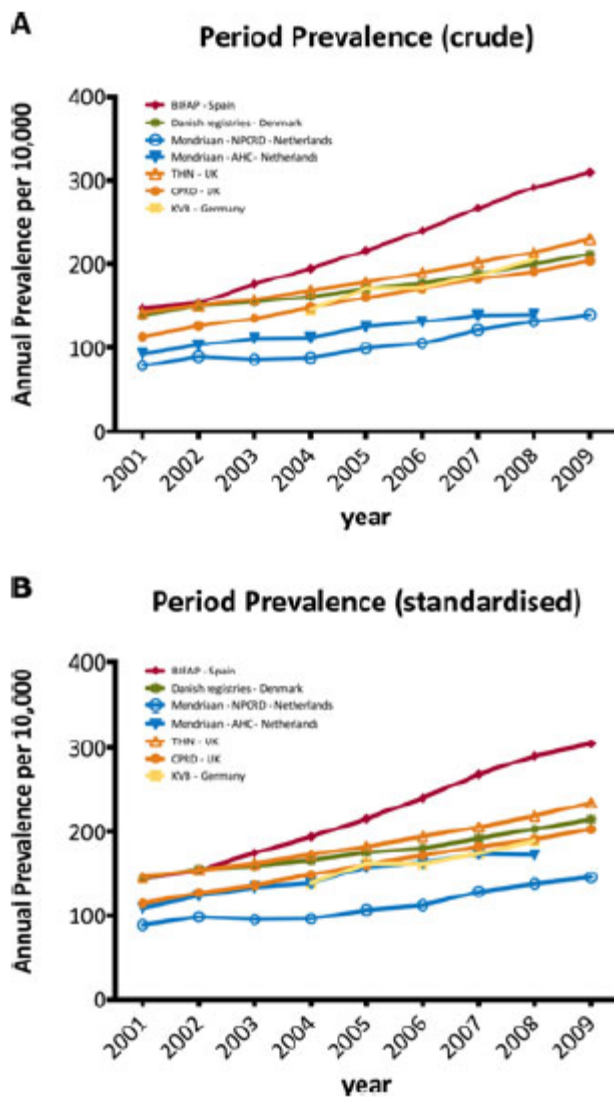
Figure 2. Annual prevalence of having any AED prescription in all countries stratified by age and sex in 2008. *In Mondriaan-AHC, prevalence in age-category 90+ was based on only three and four observations, respectively, for females and males.