Cross-national comparison of antiepileptic drug use: Catalonia, Denmark and Norway, 2007-2011

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ABSTRACT

BACKGROUND: The consumption of antiepileptic drugs (AEDs) has increased in recent years, primarily among those AEDs marketed since 1990. The purpose is to describe and compare AED consumption in Catalonia, Denmark, and Norway.

METHODS: Population-based descriptive study set in the outpatient healthcare sector. Data were retrieved from the Norwegian Prescription Register, Danish Register of Medicinal Product Statistics and DATAMART® in Catalonia, for 2007-2011. We calculated defined daily doses/1,000 inhabitants/day (DID), by age and gender. AEDs were defined according to the Anatomical Therapeutic Chemical classification (N03A). We reviewed the population covered by the databases, the drug data source and the definition of outpatient healthcare sector to compare the results across the three settings.

RESULTS: The total AED use steadily increased over the study period in the three settings. In 2011, consumption was highest in Catalonia (15.2 DID), followed by Denmark (15.1 DID) and Norway (14.2 DID). The "other AEDs" (N03AX) subgroup represented 60% of all AED use. The N03A pattern by gender did not differ across the three settings. Marked differences by age and gender appeared when studying lamotrigine, topiramate, gabapentin, pregabalin and levetiracetam. Differences among the databases occurred primarily in the definition of outpatient healthcare setting.

CONCLUSIONS: There was a rapid increase in "other AEDs" in all three settings, which explained the high use of AEDs. Drug data source, population coverage and definition of the healthcare setting were key items to understand the patterns of drug use across countries.

Key words: Cross-national comparison, drug utilisation, antiepileptic drugs, defined daily doses/1,000 inhabitants/day.

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INTRODUCTION

Since the introduction of the first antiepileptic drug (AED) to the market in 1857, multiple medicines have been developed to treat epilepsy. Indications for AED use have historically expanded to other neurological disorders [1]. Most of the AEDs marketed since the 1990s, which are known as new AEDs, were initially indicated as adjunctive therapy in patients with refractory epilepsy [2]. Currently, these new AEDs are not only recommended as monotherapy in the treatment of epilepsy [3], but some of them have also been approved for indications other than epilepsy, such as neuropathic pain and generalised anxiety [4]. Moreover, these new AEDs are increasingly prescribed off-label. In the USA, the Food and Drug Administration calculated that in 2001, up to 51% of the AEDs prescribed in the outpatient sector were for off-label indications [5].

Researchers have claimed that new AEDs have several advantages over older AEDs. They seem to be more effective in the treatment of epilepsy, and they have less severe adverse effects and drug-drug interactions [6]. However, severe adverse reactions have been described after the drugs' authorisation [7,8], including a potential increased risk of suicide [9]. In addition, the new AEDs are much more expensive than are the older ones.

These factors have increased researchers' interest in studying patterns of AED use. Some studies have focused on a single country or a restricted geographical area within one country [10-12] or on subgroups of a population [13-14]. Few studies have conducted a cross-country comparison of AED use [15-17]. The aim of this study is to describe and compare the utilisation of AEDs in Catalonia, Denmark, and Norway between 2007 and 2011.

METHODS

We analysed AED consumption in Catalonia, Denmark, and Norway by age and gender between 2007 and 2011.

We described AEDs according to the Anatomical Therapeutic Chemical (ATC) classification system, i.e., N03A. Given the differences in the available medications across the three countries, we only analysed the AEDs that were offered in all three settings. Mephenytoin, fosphenytoin, phenytoin combinations, valpromide, sultiame, felbamate, and stiripentol were excluded. These AEDs represented less than 0.1% of the total AED consumption in each country, except for valpromide in Catalonia which represented 0.4%. Retigabine was also excluded because it was approved in March 2011.

Nationwide databases provided the total number of defined daily doses (DDDs), as defined in the 2012 version of the ATC/DDD guidelines [18]. We measured the drug consumption data in DDDs/1,000 inhabitants/day (DIDs). DID were calculated according to the following formula: (DDD[mg]*1,000)/(Total number of inhabitants*365 [day]). We calculated DIDs by 10-year age groups and gender. We retrieved the total number of inhabitants by age groups and gender from the national official statistics webpages [19-21].

We conducted all analyses in Microsoft® Excel 2007 (Microsoft Corporation, Redmond, WA, USA).

To help compare the AED consumption across the three settings, we considered the population coverage of the database, drug data source or drug coverage, and the definition of the outpatient healthcare setting to be potential sources of biases when comparing the results. Table 1 contains a description of the drug data providers, population covered by the databases, and sources of drug-consumption data.

RESULTS

General Overview of AED use

During the period 2007-2011, the overall use of AEDs increased from 11.9 DID to 15.2 DID in Catalonia; from 12.1 to 15.1 DID in Denmark; and from 11.2 to 14.2 DID in Norway. These changes corresponded to average percentage increases of 27.3%, 24.6%, and 27.2% over the study period in Catalonia, Denmark, and Norway, respectively.

At ATC level 4, the subgroup "other AEDs" (N03AX) consumption represented more than 50% of all AED consumption in all three settings over the whole study period. Within this group, the percentage variation of DIDs between 2007 and 2011 showed an increase by 54.3%, 66%, and 61.4% from the original level in Catalonia, Denmark and Norway, respectively. The

TABLE 1

CHARACTERISTICS OF THE NATIONWIDE ADMINISTRATIVE DRUG CONSUMPTION DATABASES

COUNTRY	DATA PROVIDER	DATABASE	DATA SOURCE[a]	POPULATION COVERAGE[b]. [TOTAL NUMBER OF INHABITANTS IN 2011]
Catalonia http://www20.gencat.cat/portal/site/salut/menuitem.003a2436be9bc6ec3bfd8a10b0c0e1a0/?vgnextoid=17f0215e97ada310VgnVCM1000008d0c1e0aRCRD&vgnextchannel=17f0215e97ada310VgnVCM1000008d0c1e0aRCRD&vgnextfmt=default	CatSalut. Catalan Health Service (Application to the data provider)	DATAMART	Reimbursed	99% [7 432.830]
Denmark www.medstat.dk	The Danish Health and Medicines Authority (Online)	Register of Medicinal Product Statistics	Dispensed	100% [5 570.796]
Norway www.norpd.no	Norwegian Institute of Public Health (Online)	Norwegian Prescription Database	Prescribed	100% [4 920.305]

[a]Reimbursement: medicines prescribed by a healthcare professional, dispensed by a pharmacist and reimbursed by a healthcare provider. It excludes over-the-counter medicines and those prescription-only-medicines that are not reimbursed. Dispensation: medicines dispensed by the pharmacy to the patient either prescribed or not. It includes over-the-counter medicines. Prescription: prescribed medicines dispensed to patients either reimbursed or not. It does not include over-the counter medicines, except if there is an authorised indication for which these OTC medicines may be prescribed. [b] Proportion of the resident population registered in the database. All websites were last accessed on 17 September 2013.

consumption of the rest of subgroups either remained stable (succinimide [N03AD] and fatty acid derivatives [N03AG]) or showed a negative percentage variation trend over the 5-year study period (hydantoin derivatives [N03AB], benzodiazepine derivatives [N03AE], and carboxamide derivatives [N03AF]) (see Table 2).

Overall, there is a similar pattern of AED use by age and gender in the three settings over the study period. The consumption of "other AEDs" increased with increasing age, reaching a maximum at 50-59 years in the Nordic countries and two decades later in Catalonia. For the rest of the ATC subgroups, consumption by age followed a similar pattern. However, it showed slight variations in the decade at which the maximum was reached (data not shown). Although the overall consumption of AEDs was higher in men than in women, in the "other AEDs" subgroup, consumption was higher among women than men. This distribution by gender was similar in all three settings (see Figure 1).

Individual AED use

We focused on lamotrigine, gabapentin, pregabalin, levetiracetam, and topiramate because their consumption steadily increased over the study period and because there were remarkable differences among the three settings (Figure 2). The most striking differences in terms of DID were the consumption of lamotrigine, which was approximately 4.5 times higher in Denmark and Norway than it was in Catalonia, and the consumption of topiramate, which was 3.2 times higher in Catalonia than it was in the Nordic countries. The consumption of levetiracetam increased by 181.2%, 81.9%, and 60.4% in Catalonia, Denmark, and Norway, respectively, from 2007 to 2011.

In Catalonia, by 2010, levetiracetam use showed a curve with a steep slope at 40-49 years for men. This curve became sharper in 2011. We also observed a similar pattern for women that occurred a decade later, with the absolute DID numbers being slightly

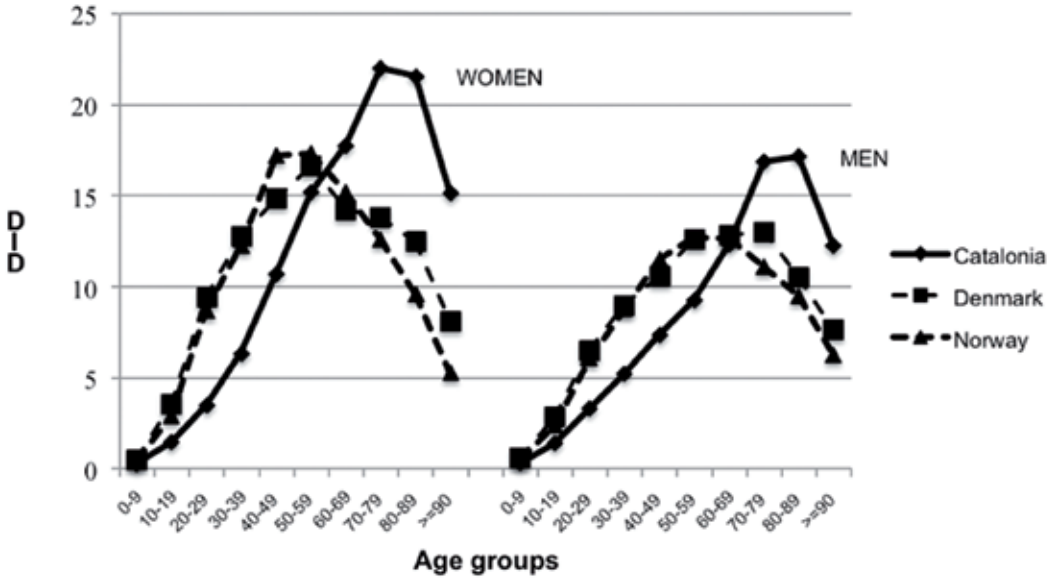
TABLE 2

AED CONSUMPTION IN CATALONIA, DENMARK AND NORWAY STRATIFIED BY DRUG GROUP, FOR YEARS 2007 AND 2011. EXPRESSED IN DDD/1,000 INHABITANTS/DAY.

	CATALONIA		DENMARK		NORWAY	
	2007	2011	2007	2011	2007	2011
OVERALL AED USE (N03A)	11.9	15.2	12.1	15.1	11.2	14.2
BARBITURATES AND DERIVATIVES (N03AA)	0.9	0.8	0.7	0.5	0.6	0.4
HYDANTOIN DERIVATIVES (N03AB)	0.9	0.7	0.2	0.2	0.5	0.3
SUCCINAMIDE DERIVATIVES (N03AD)	0.0	0.0	0.0	0.0	0.0	0.0
BENZODIAZEPINE DERIVATIVES (N03AE)	0.8	0.9	0.7	0.5	0.7	0.6
CARBOXAMIDE DERIVATIVES (N03AF)	2.1	2.1	3.0	2.5	2.3	2.0
FATTY ACID DERIVATIVES (N03AG)	1.5	1.7	1.7	1.7	1.5	1.6
OTHER ANTIEPILEPTIC DRUGS (N03AX)	5.8	8.9	5.8	9.7	5.8	9.3

FIGURE 1

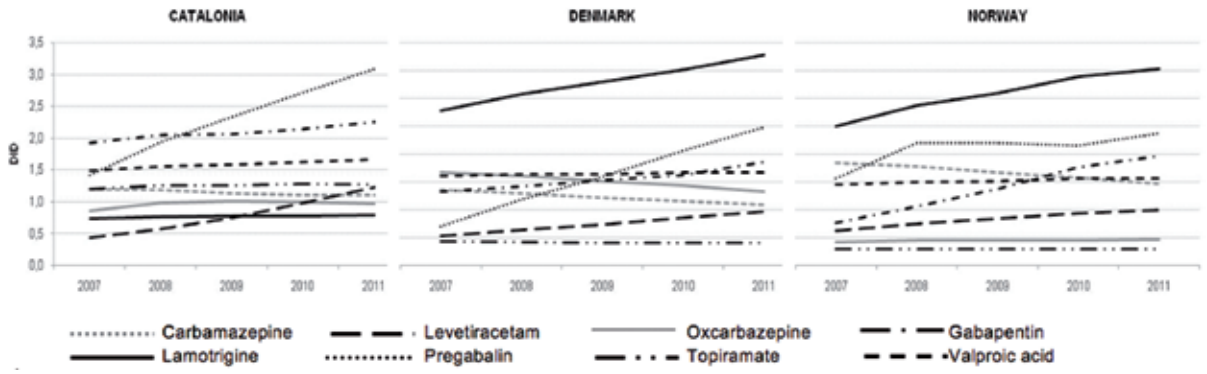
"OTHER AEDS" GROUP CONSUMPTION IN CATALONIA, DENMARK, AND NORWAY BY AGE AND GENDER, YEAR 2011.



higher in men than they were in women (data not shown). Levetiracetam use in Nordic countries showed a 2-spiked curve, with one peak between 10 and 29 years of age and a second peak between 60 and 79 years of age. In Denmark, there was a transition in the consumption of pregabalin to a much younger age in 2011, with the primary use occurring in women (data not shown). In Norway, gabapentin was mainly consumed in the 50- to 70-year-old group in women, whereas in men, the consumption was highest for those over 60 years old. See Figures 3, 4, and 5 in the supplementary material for a detailed description on individual "other AEDs" consumption by age and gender, in Catalonia, Denmark and Norway, respectively, for the year 2011.

FIGURE 2

MOST CONSUMED AEDS IN CATALONIA, DENMARK, AND NORWAY, BY YEAR (2007-2011).



DISCUSSION

This study showed the increased utilisation of AEDs between 2007 and 2011 in Catalonia, Denmark, and Norway, and this increase primarily occurred because of the increase within the "other AEDs" subgroup. The differences across countries arose when we compared the patterns of use by age, gender, and individual medicines, with a clear differentiation observed between the Nordic countries and Catalonia. Lamotrigine, gabapentin, pregabalin, topiramate, and levetiracetam were the most consumed AEDs in the three settings. The distribution by age showed an increased consumption of gabapentin and pregabalin among the elderly. In middle-aged groups, lamotrigine in the Nordic countries and topiramate in Catalonia were the most used AEDs. Levetiracetam consumption greatly increased over the study period in all three settings. Women were the main users of the "other AEDs" subgroup.

Taking the European Drug Utilisation Group work [22] and the work developed by the European Surveillance Antimicrobial Consumption (ESAC) group [23] as a starting point, we considered three key items to interpret the differences in AED use across countries.

First, the drug data providers and data sources are diverse, thus rendering comparison across countries, healthcare settings, or time difficult. In this study, AEDs were prescription-only medicines in all three settings and were all reimbursed by the national health systems throughout the study period. We believe that any variations in AED consumption that were introduced by the different sources of drug data would be minor.

A second item is the population coverage of these databases. Although all databases covered the entire resident population in each setting, several specificities linked to the organisation of each of the health systems may have influenced the results presented in this study. In Catalonia, civil servants may opt out of the national health insurance system. Furthermore, in 2010, approximately 26.4% of the Catalan population was double-covered by a private-for-profit insurance [24]. The Catalan database does not include the prescriptions issued by private doctors or doctors under alternative health insurers. In Norway, private-for-profit health insurance is estimated to cover approximately 5% of the population, and this insurance usually plays a complementary role [25]. In Denmark, there is no possibility of opting out of the system [26]. Consequently, our calculations may have underestimated the AED consumption in Catalonia.

Finally, the definition of the outpatient healthcare setting. For this group of medications, we were interested in learning whether the AEDs consumed in nursing homes (NHs) were included as outpatient medication in the database. Surveys conducted in Italy, Sweden, and Germany showed that between 4.3% and 12.2% of the institutionalised elderly population used AEDs [27,28,29]. In Denmark and Catalonia, medicines were registered to the patients through the pharmacy, not the NH. However, in Norway, the data downloaded from the website did not include NHs. Thus, AED consumption might have been underestimated among elderly age groups in Norway.

Overall, the consumption of AEDs could have been underestimated in Catalonia and among the elderly in Norway due to the data-collection methods. However, the above-mentioned factors are not the only ones that can affect cross-country comparisons. Cultural differences [30], variations in the prevalence of the diseases treated by AEDs, national or regional clinical therapeutic guidelines [31], reimbursement policies [32], advertising policies [33], and safety warnings [34] may influence the inter-country variations in AED use.

Several published studies support our results, although conducted in different study periods. In Denmark (1993-2002) [10], Norway (2004-2009) [35], Italy (2000-2005) [14], and the United Kingdom (1993-2007) [36], the authors observed an increased consumption of AEDs, that was primarily due to new AEDs. We do not know of any study reporting AED consumption in Catalonia; however, data from the Spanish Ministry of Health between 1992 and 2006 showed an upward trend in the consumption of the "other AEDs" subgroup [37]. There is a difference between new AEDs and "other AEDs" subgroup. AEDs marketed after 1990 are generally classified as new AEDs. All AEDs included in the "other AEDs" subgroup also entered the market after 1990. However, eslicarbazepine, oxcarbazepine, tiagabine, and vigabatrin, which are also considered new AEDs, were not classified in the "other AEDs" subgroup. However, in our study, these four medicines, showed a steady or downward trend in their use between 2007 and 2011. Even if new AEDs and "other AEDs" are not interchangeable groups, we believe that the inclusion of the four above-mentioned AEDs in the group of new AEDs in the cited studies, still support our results.

The trends in the "other AEDs" subgroup consumption by age differed among the 3 settings. In Catalonia, patients 60 years of age and over consumed 46% of the "other AEDs" subgroup. In Denmark and Norway, there was a shift towards younger ages: patients aged between 40 and 59 years of age consumed 38.9% and 42.4%, respectively,of the"other AEDs". Two studies, one conducted in southern Italy (2004-2007) [14] and another conducted in the USA (2000-2004) [38], showed that AEDs such as phenytoin were still highly prescribed among the elderly, although newer AEDs exhibited an increase in use over the study period.

In our study, the use of the "other AEDs" was highest among women, whereas the consumption of the remaining AEDs subgroups was highest among men in all 3 settings. Several authors have linked these gender differences to different indications for AED use. For epilepsy, consumption is slightly higher in men than it is in women [35,39,40], and is linked to the use of old AEDs [11], while women account for a higher percentage of users of the new AEDs associated with mood disorders and pain [11].

Treatment with lamotrigine was highest among women between 20 and 70 years of age in Norway and Denmark, whereas in Catalonia, topiramate was the most used AED among female adults (20 to 70 years of age). The results obtained from the Nordic countries for lamotrigine are in line with other study results obtained in Germany [12], the Netherlands [41], and the United Kingdom [36]. Conversely, no published studies were found reporting a similar pattern of topiramate use compared with that found in Catalonia. The most likely explanation for these discrepancies in the topiramate and lamotrigine consumption across the 3 settings may be the potential prescription of these medicines for disorders other than epilepsy [10,42] and for off-label uses. Several articles have reported the efficacy of topiramate for off-label uses [43,44] and of lamotrigine for people with dementia [45]. A rapidly increasing use of levetiracetam (first authorised in 2000 by the European Medicines Agency) over the study period was also observed in most of the above-cited studies.

This study described and compared AED consumption in three settings using population-based databases. Another strength of this study was the use of the ATC/DDD methodology, which allowed us to aggregate drug data, independent of the strength and dosage form. Moreover, because of the chronic use of AEDs, the results that were reported as DIDs reflected the proportion of the population exposed to AEDs by age groups and gender. However, we did not have information on the actual redemption and intake of AEDs, i.e., patient compliance.

The main weakness of this study was the lack of information on specific indications for use. Having this information would have helped us understand the observed differences in AED consumption across the three settings. Another limitation was the use of aggregated data, which

made it impossible to study monotherapy/polytherapy as proxies for indication of use. The DDD is a technical unit that, in this study, represented the assumed average daily dose for epilepsy in adults. Thus, this study did not consider the other approved indications, which may have prescribed daily doses that may substantially differ from the assigned DDD.

CONCLUSIONS

Pregabalin, gabapentin, lamotrigine, topiramate and levetiracetam are highly used, but there are dramatic differences among countries, which raises concerns about the appropriateness of these drugs' use. A study on AED consumption at the individual level that focuses on the indications for use of these medications, potentially using clinical databases, which contain more detailed information should be performed.

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