

FULL-LENGTH ORIGINAL RESEARCH

Comparison of antiepileptic drug prescribing in children in three European countries

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SUMMARY

Purpose: Antiepileptic drug (AED) use in young people is increasing. However, evidence of its use at a multinational level is limited. This study aims to characterize AED prescribing in the young in three European countries and to assess the capacity of drug safety surveillance.

Methods: A retrospective cohort study was conducted in 2001–2005 using primary care databases: PEDIANET (Italy, 0–11 years), IPCI (The Netherlands, 0–18 years), and IMS Disease Analyzer (United Kingdom, 0–18 years). Prescribing prevalence was calculated by country, patient age, and drug type.

Results: In 2005, AED prevalence in children (0–11 years) was highest in Italy [3.9 subjects/1,000 person-years (PY)] followed by the United Kingdom (3.0 subjects/1,000 PY) and The Netherlands (2.2 subjects/1,000 PY). Over the study period, prescribing prevalence in 0–11 year olds was

stable in all countries. In contrast, a steady rise of AED prevalence was observed in adolescents (12–18 years) in the United Kingdom ($p = 0.0003$) but not in The Netherlands ($p = 0.88$). All countries showed a slight increase in prevalence for newer AEDs. Simultaneously, the prevalence of conventional AEDs decreased in The Netherlands and Italy, but not in the United Kingdom. In 2005, lamotrigine use was highest in The Netherlands and the United Kingdom, whereas topiramate was favored in Italy.

Discussion: In Europe, conventional AEDs are still the main treatment choice for children with epilepsy, and the use of newer AEDs remains low. Our study highlights a lack of research capacity to conduct multinational AED safety studies in children. Further work should explore large databases and other health care settings to meet these research needs.

KEY WORDS: Antiepileptic drugs, Pharmacoepidemiology, Prevalence, Children, Adolescents.

Epilepsy is one of the most common neurologic disorders in childhood. It is estimated that the annual incidence rate of childhood-onset epilepsy is 61–124 per 100,000 in developing countries and 41–50 per 100,000 in developed countries (Guerrini, 2006). In the majority of children with epilepsy, pharmacotherapy is still the main treatment option. During the last decade, several newer antiepileptic drugs (AEDs) have been introduced for epilepsy treatment in clinical practice (Macleod & Appleton, 2007). Ackers et al. (2007) used the United Kingdom General Practice Research Database (GPRD) and has shown a 5-fold increase of newer AED pre-

scribing in youths aged <19 years between 1993 and 2005. In response to the rapid uptake of the newer AEDs in the United Kingdom, particularly lamotrigine, topiramate, and levetiracetam, the authors suggested that further research should be prioritized on the safety of these drugs due to the limited data available at present. Similarly, a Dutch study using a pharmacy prescription database (InterAction database) has also reported that the use of lamotrigine among youth aged 0–19 years has increased between 1997 and 2005 (van de Vrie-Hoekstra et al., 2008). Another study analyzed data from the United Kingdom Committee on Safety of Medicines Yellow Card Scheme and reported that AEDs were the drugs most likely to be associated with suspected fatal adverse drug reaction reports. The newer AEDs (e.g., vigabatrin, lamotrigine, topiramate, and gabapentin) accounted for about 30% of 65 antiepileptic-treated death cases (Clarkson & Choonara, 2002). Because many AEDs have not been well tested in children, the European

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Medicines Agency (EMA) suggests that more research into the efficacy and safety of newer AEDs is needed (EMA, 2008). Although the data from the United Kingdom are a useful starting point to prioritize the research, the uptake of the newer AEDs in other countries is still not clear. Furthermore, there is a need to understand the extent of AED prescribing in this population at a multinational level. A multinational prevalence comparison would be a useful means for elaborating capacity and further research on AED safety surveillance. Therefore, we conducted a retrospective cohort study to compare AED prescribing prevalence in children and adolescents aged 0–18 years within three European countries (Italy, The Netherlands, and the United Kingdom).

METHODS

Data source

Primary care databases from three different countries (United Kingdom, Italy, and The Netherlands) were used to retrieve data, which were analyzed according to a standard protocol. The following details describe each database at the time of study commencement. The data from the United Kingdom were derived from the IMS Disease Analyzer (IMS DA) (Murray et al., 2005; Hsia et al., 2009; Thompson et al., 2009). This database contains approximately 3 million anonymous patient records from about 570 general practitioners (GPs) (Wong & Murray, 2005; Neubert et al., 2008). Information in the IMS DA includes patient demographics, diagnoses, symptoms, prescription details, referrals, and laboratory tests. Data from The Netherlands were retrieved from the Integrated Primary Care Information (IPCI) database. This database contains more than 1,000,000 patients from 150 GPs. Information in the IPCI includes anonymous patient records, diagnoses and symptoms, prescriptions with ICPC-coded (International Classification for Primary care) indication, dosage regimen, referrals, laboratory tests, and hospitalizations (van der Lei et al., 1993; Vlug et al., 1999; 't Jong et al., 2002; Verhamme et al., 2005; Van Soest et al., 2008). The data from Italy were obtained from the PEDIANET; this pediatric database contains anonymous patient records for about 180,000 children provided by 105 primary care pediatricians. The PEDIANET contains data including diagnoses, symptoms, prescriptions, medical examinations, referrals, and hospitalizations (Menniti-Ippolito et al., 2000; Nicolosi et al., 2003; Sturkenboom et al., 2005). All three databases comprise the complete automated medical records from physicians in primary care settings. In all three countries children need to be registered with a GP (the United Kingdom and The Netherlands) or a pediatrician (Italy); hence all three databases are population based. Data are recorded for children and adolescents aged 0–18 years in The Netherlands and the United Kingdom, whereas data were available only up to the age of 14 years in Italy. Prescribed drugs in

the PEDIANET and IPCI databases are coded based on the World Health Organization (WHO)-Anatomical Therapeutic Chemical (ATC) classification (WHO, 2008). Prescriptions held in the IMS DA database are coded based on the ATC classification issued by the European Pharmaceutical Market Research Association (EphMRA, 2008). A comparative study has been previously conducted and has demonstrated that data are comparable in all three databases (Sturkenboom et al., 2008).

Study population

The study population was defined as children and adolescents aged 0–18 years registered with a GP who contributed data to the databases between January 1, 2001 and December 31, 2005. Age was assessed on 1 January of each year and grouped according to the guidelines of the International Conference of Harmonization (ICH) as aged <2, 2–11, and 12–18 years (Rose & Stotter, 2007). All study subjects had to have at least 6 months of research standard data and received at least one prescription for an AED during the study period.

Data analysis

AEDs were defined based on the therapeutic level ATC-N03 and further subgrouped as conventional and newer AEDs. The conventional AEDs included any of the following: barbitone, carbamazepine, clonazepam, ethosuximide, phenobarbital, phenytoin, primidone, and valproic acid. The newer AEDs included any of the following: felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, and vigabatrin. It should be noted that the availability of AEDs on the market differs between countries; therefore, not every AED is prescribed in all three countries. We excluded medication such as diazepam and midazolam, which are prescribed for the treatment of prolonged seizures or status epilepticus.

Prevalence was defined as the number of subjects with at least one AED prescription during the year of investigation divided by the total number of person-years in the same year stratified by age, and was calculated using the Poisson distribution with a 95% confidence interval (CI). Prevalence was calculated by age, calendar year and drug type (conventional vs. newer AEDs). We also analyzed the frequency of AEDs prescribed for children and adolescents with an indication/diagnosis of epilepsy for all three databases together. Due to the absence of adolescent data in PEDIANET, prevalence of AED use for comparison in three countries was estimated for children aged 0–11 years only. As for the adolescent group (ages 12–18 years), data from The Netherlands and the United Kingdom were analyzed separately.

The chi-square test (Cochran-Armitage test for trend) was used to examine the yearly trend of AED prescribing. Statistical analyses were conducted using STATA/SE version 9.1 (Stata Corp., College Station, TX, U.S.A.). Ethical

approval was granted from the Independent Scientific and Ethical Advisory Committees of all three databases.

RESULTS

The total population comprised 641,670 patients contributing to a total of 1,975,615 person-years in three databases between 2001 and 2005. In 2005, there were 405 children aged 0–11 receiving conventional AEDs and 169 receiving newer AEDs in the United Kingdom. The number of users of conventional AEDs was 278 in Italy and 46 in The Netherlands. The number of newer AED users was 97 in Italy and 17 in The Netherlands. Table 1 shows the distribution of AED use in children aged 0–11 in the three databases by AED type, age, gender, and country.

As shown in Fig. 1, in 2005 the prevalence of AED prescribing in children aged 0–11 years was highest in Italy (3.9 subjects per 1,000 person-years) followed by the United Kingdom (3.0 subjects per 1,000 person-years) and exceeded that of The Netherlands (2.2 subjects per 1,000 person-years). During the study period the prevalence of AED prescribing in those aged 0–11 years was relatively stable, with no significant increase in all three countries. In contrast, a steady increase of the AED prevalence was observed in adolescents, with a significant change in the United Kingdom ($p = 0.0003$), but not in The Netherlands ($p = 0.88$) (Fig. 2).

Table 2 shows the use of AEDs for the treatment of epilepsy in the three countries. The most commonly pre-

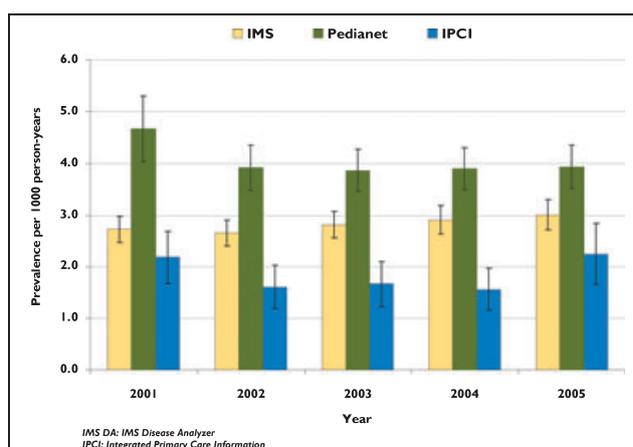


Figure 1.

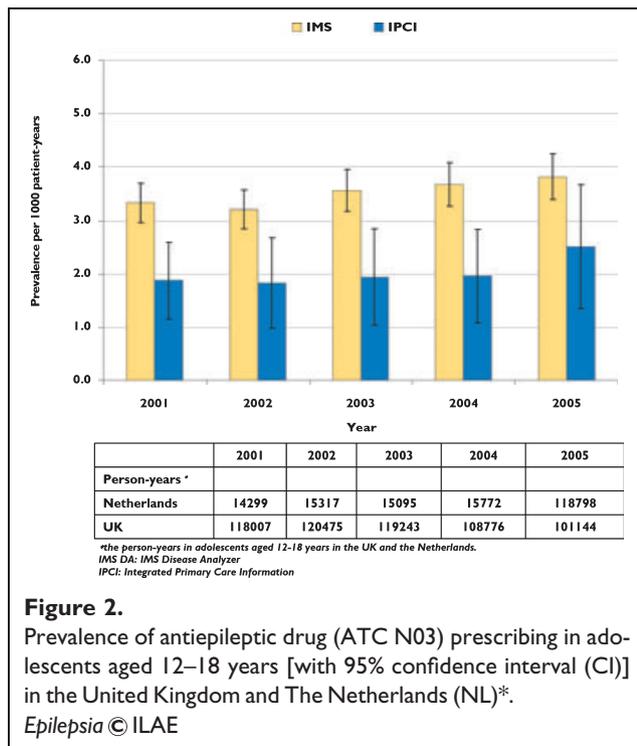
Prevalence of antiepileptic drug (ATC N03) prescribing in children aged 0–11 years [with 95% confidence interval (CI)] from three countries [the United Kingdom, Italy, and The Netherlands (NL)].

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scribed AEDs for the treatment of epilepsy were valproic acid, carbamazepine, and lamotrigine in those aged 2–18 years. In the youngest age group (aged <2 years), the most commonly prescribed AEDs were valproic acid, phenobarbital, carbamazepine, vigabatrin, and topiramate. A prescribing change was observed during the study period. In 2001, 7 children with epilepsy aged <2 years

Table 1. Characteristics of study subjects aged 0–11 years by antiepileptic drug (AED) type and country between 2001 and 2005 (Italy, The Netherlands, and United Kingdom)

	Italy (aged 0–11)			The Netherlands (aged 0–11)			United Kingdom (aged 0–11)		
	Boys	Girls	Total	Boys	Girls	Total	Boys	Girls	Total
Conventional AEDs									
Number of subjects									
2001	98	89	187	31	33	64	224	222	446
2002	149	119	268	25	28	53	217	210	427
2003	169	133	302	26	26	52	227	205	432
2004	157	149	306	27	23	50	209	204	413
2005	139	139	278	23	23	46	217	188	405
Newer AEDs									
Number of subjects									
2001	20	21	41	5	10	15	87	79	166
2002	30	39	69	4	9	13	99	70	169
2003	43	45	88	9	8	17	91	78	169
2004	48	49	97	6	7	13	82	87	169
2005	50	47	97	8	9	17	75	94	169
Person-years									
2001	22,862.7	21,100.5	43,963.2	16,763.5	15,949.8	32,713.3	86,417.7	82,058.7	1,68,476.5
2002	39,488.7	36,512.8	76,001.6	18,043.4	17,096.3	35,139.8	84,763.6	80,425.2	1,65,188.9
2003	46,790.2	43,212.6	90,002.9	17,702.5	16,737.5	34,440.0	82,426.3	78,415.6	1,60,842.0
2004	47,012.0	43,237.4	90,249.5	18,102.3	17,250.4	35,352.8	77,076.3	73,367.1	1,50,443.5
2005	43,268.3	39,715.4	82,983.8	12,757.9	12,270.6	25,028.5	74,086.5	70,694.7	1,44,781.3



received phenobarbital (29% of AED-treated subjects), 10 received valproic acid (42%), and 3 received vigabatrin (13%). In 2005, the use of phenobarbital decreased to 6% (n = 1), whereas vigabatrin increased to 31% (n = 5). The more recently marketed drugs topiramate and levetiracetam had the largest increase in use for children aged 2–11 years (p = 0.06 for topiramate and p = 0.001 for levetiracetam) and adolescents aged 12–18 years (p = 0.04 for topiramate and p = 0.03 for levetiracetam) between 2001 and 2005.

The prevalence of conventional AEDs was higher in Italy than in the United Kingdom and The Netherlands (Fig. 3). In 2005, the prevalence of conventional AED prescribing was 3.35 subjects per 1,000 person-years in Italy, 2.80 subjects per 1,000 person-years in the United Kingdom, and 1.84 subjects per 1,000 person-years in The Netherlands. When comparing the prescribing prevalences of conventional and newer AEDs over time, it was apparent that conventional AEDs were favored over newer AEDs in all three countries in children aged 0–11 years (Fig. 3). There was a slight increase in prevalence in all three countries for newer AEDs. The prevalence of newer AED prescribing was lower in The

Table 2. Distribution of antiepileptic drugs use in children and adolescents with epilepsy diagnosis in three countries

	2001						2005					
	<2 years		2–11 years		12–18 years		<2 years		2–11 years		12–18 years	
	N	%	N	%	N	%	N	%	N	%	N	%
Barbiturates												
Phenobarbital	7	29	10	2	2	1	1	6	13	3	3	1
Primidone	–	–	–	–	1	0	–	–	2	0	1	0
Hydantoin derivatives												
Phenytoin	1	4	6	1	4	1	2	13	2	0	2	1
Succinimide derivatives												
Ethosuximide	–	–	6	1	9	2	–	–	11	3	8	2
Benzodiazepine derivatives												
Clonazepam	–	–	10	2	9	2	–	–	7	2	5	1
Carboxamide derivatives												
Carbamazepine	3	13	115	28	111	30	2	13	87	21	102	26
Oxcarbazepine	–	–	1	0	5	1	–	–	9	2	4	1
Fatty acid derivatives												
Valproic acid	10	42	217	54	167	46	5	31	230	55	182	46
Vigabatrin	3	13	10	2	6	2	5	31	5	1	3	1
Tiagabine	–	–	2	0	1	0	–	–	1	0	–	–
Other												
Lamotrigine	1	4	60	15	88	24	–	–	54	13	105	26
Topiramate	–	–	13	3	7	2	4	25	39	9	22	6
Gabapentin	–	–	4	1	5	1	–	–	1	0	8	2
Levetiracetam	–	–	–	–	–	–	–	–	13	3	11	3
Pregabalin	–	–	–	–	–	–	–	–	–	–	1	0
Felbamate	–	–	–	–	–	–	–	–	1	0	–	–
Total^a	24	100	404	100	365	100	16	100	421	100	400	100

^aThe number of children treated for epilepsy in the specific age category. The sum of column percentages may exceed the total, since children may use more than one type of antiepileptic drug.

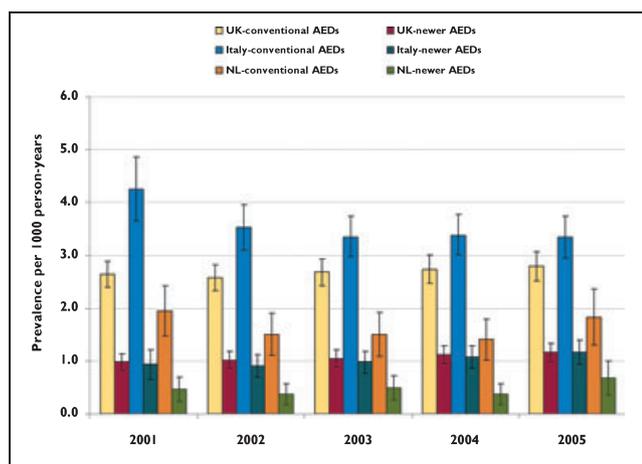


Figure 3. Prevalence of conventional and newer antiepileptic drug prescribing in children and adolescents aged 0–11 [with 95% confidence interval (CI)] in three countries [the United Kingdom, Italy, and The Netherlands (NL)].

Epilepsia © ILAE

Netherlands compared to the United Kingdom and Italy during the study period.

Table 3 shows all children who received AEDs regardless of the indication in 2005. There were variations in the newer AEDs used in children aged 0–11 years within the three countries (Table 3). Topiramate was favored over the other newer AEDs in Italy in 2005, with a prescribing prevalence of 0.49 subjects per 1,000 person-years. In The Netherlands, lamotrigine was the most commonly prescribed newer AED (0.28 subjects per 1,000 person-years), followed by oxcarbazepine and gabapentin. Lamotrigine was also the most commonly prescribed newer AED in the United Kingdom (0.55 subjects per 1,000 person-years); however, the prevalence was about twice as high as that in The Netherlands

(0.25 subjects per 1,000 person-years). Pregabalin was prescribed in The Netherlands only, and felbamate was prescribed in Italy only.

DISCUSSION

Our data show that conventional AEDs still dominate the prescribing of AEDs in children, and that the use of newer AEDs as well as the overall prevalence of AED prescribing in children aged 0–11 years remains relatively stable. A significant increase of AED prescribing was observed only in United Kingdom adolescents aged 12–18. The overall AED prescribing in our study is in line with the study using Dutch pharmacy dispensing data (van de Vrie-Hoekstra et al., 2008). The authors reported that conventional AEDs dominated the usage in children and adolescents aged 0–19 years between 1997 and 2005.

In contrast to the United Kingdom study by Ackers et al. (2007), our study does not show a rapid uptake of the newer AEDs in children during the study period. Two reasons may explain this difference. First, clinicians are more conservative when treating younger children with newer AEDs compared to the adolescents, hence the increase of newer AED prescribing is less significant when only investigating the 0–11 age group. Secondly, lamotrigine was the most commonly prescribed newer AED in the United Kingdom study, with the fastest rate of uptake of its use before the year 2000, which is prior to our study period (Ackers et al., 2007). However, due to the different age structure, databases, and study periods across the studies, a direct comparison of the studies is difficult (Ackers et al., 2007; van de Vrie-Hoekstra et al., 2008). It should also be noted that the data we used in this study were collected from primary care settings. Prescriptions of the newer AEDs are normally initiated by specialists and followed by GPs (Wong et al., 1999a); therefore, there may be a slight underestimation of the true prescribing prevalence.

Table 3. Prevalence with 95% CI of newer antiepileptic drug use in children aged 0–11 years in 2005 in three countries (Italy, The Netherlands, and United Kingdom)

	Italy		The Netherlands		United Kingdom	
	N	Prevalence	N	Prevalence	N	Prevalence
Felbamate	1	0.01 (0.004–0.06)	0	NA	0	NA
Gabapentin	0	NA	5	0.20 (0.006–0.15)	8	0.06 (0.02–0.09)
Lamotrigine	21	0.25 (0.14–0.36)	7	0.28 (0.07–0.49)	79	0.55 (0.43–0.66)
Levetiracetam	16	0.19 (0.10–0.24)	2	0.08 (0.02–0.29)	21	0.15 (0.08–0.21)
Oxcarbazepine	18	0.22 (0.12–0.32)	5	0.20 (0.09–0.47)	4	0.03 (0.001–0.05)
Pregabalin	0	NA	1	0.04 (0.007–0.23)	0	NA
Tiagabine	0	NA	0	NA	2	0.01 (0.002–0.04)
Topiramate	41	0.49 (0.34–0.65)	1	0.04 (0.007–0.23)	41	0.28 (0.20–0.37)
Vigabatrin	13	0.16 (0.07–0.24)	2	0.08 (0.02–0.29)	14	0.10 (0.04–0.15)

^aPrevalence was expressed as subjects per 1,000 person-years.

^bNA, not available; no case was being given newer antiepileptic drugs.

It is evident from our data that AED prescribing varies between countries, particularly with respect to newer AED use in children. There are several reasons that may cause this difference among countries. One of the reasons for the variation of newer AED prescribing is differences in health-care systems. In 2005, no felbamate was prescribed in the United Kingdom and The Netherlands to those aged 0–11 years; however, it was still prescribed in Italy. The data in Italy were collected from primary care pediatricians, who may be more confident in using felbamate than GPs in The Netherlands and United Kingdom. Differences in epilepsy treatment guidelines may be another explanation for this prescribing difference. A study comparing United Kingdom and U.S. guidelines on the use of newer AEDs for newly diagnosed epilepsy clearly demonstrated a discrepancy between the guidelines (Beghi, 2004). However, at present there is very little information available to explain the difference in AED prescribing. Other reasons such as differences in referral patterns, prescribing habits, the availability of AEDs, length of AED therapy, and reimbursement system also need to be taken into consideration. With respect to the reimbursement system, the Dutch Health Care Insurance Board will for instance only fully reimburse the cost of a newer AED after its use is approved in The Netherlands (Knoester et al., 2004). This of course will also impact prescribing rates and could explain lower prevalence rates in The Netherlands.

Although the conventional AEDs are still the main treatment choice, in recent years many newer AEDs have been introduced into the clinical practice of epilepsy treatment. In the United Kingdom, data from a prescribing cost analysis have shown that newer AEDs accounted for 69% of total cost of all AED prescriptions (£99 million/£142 million) in 2002 (NICE, 2004). According to this figure, it is difficult to determine the proportion related to children. However, it implies the costs of newer AEDs in clinical practice are increasing. Therefore, because most newer AEDs are expensive, their cost-effectiveness needs to be taken into account when selecting newer AEDs for epilepsy treatment.

Previous studies have shown that in general newer AEDs may have more acceptable safety profiles than conventional AEDs (Wong & Lhatoo, 2000; Perucca, 2005). However, the EMEA Paediatric Working Party assessed the medication needs for epilepsy and has defined an overall need for safety data on long-term use (including effects on cognition) and the need to study efficacy and safety for younger age categories (EMEA, 2008). Although the level of newer AED use was relatively low in our study, some of the newer AEDs were still given to children below the recommended age (e.g., topiramate in children <2 years). We observed that more than 50% of children with epilepsy who were younger 2 years of age were prescribed valproic acid or vigabatrin, although prescribing guidance suggests that valproic acid should be used with caution in children younger than the age of 3 due to hepatic toxicity (Paediatric Formulary

Committee, 2007). Vigabatrin is known to cause visual field constriction in adults and serious psychiatric reactions (Wong et al., 1997a,b), and the effect on children has not been fully established. Monotherapy use is restricted for infantile spasms only (Paediatric Formulary Committee, 2007). The preceding results show that more research is urgently needed to make the treatment of epilepsy in young children safer.

In the recent years, pediatric pharmacovigilance research has rapidly advanced, particularly with the application of electronic clinical records such as the databases used in the present study. Previous studies have demonstrated that such databases can be successfully used in the investigation of adverse drug reactions (Verhamme et al., 2005; Clayton et al., 2008). Hence, it would be possible to conduct pharmacovigilance studies using these databases to investigate the safety of the newer AEDs in children. However, this study clearly demonstrates the inability to conduct a population-based safety study on newer AEDs in young children in a single European country. The number of children exposed to newer AEDs in the present population is too small to conduct a meaningful study. In 2005, there were approximately 250,000 young people aged 0–11 years covered by the three databases. Of these, only 283 children between 0 and 11 years were prescribed newer AEDs. Clearly because of this small sample size, it is not feasible to conduct an AED safety study in young children. A recently published study has demonstrated that there are more databases in Europe available for pediatric safety studies and it is possible to increase the sample size up to about 4 million children by including more databases (Neubert et al., 2008). Therefore, further research should explore the possibility of conducting a multinational AED safety study using a combination of large clinical databases. Alternatively, further work could focus on conducting multinational studies of newer AEDs in secondary and tertiary healthcare settings similar to previous adult studies to meet the research needs in children with epilepsy (Wong et al., 1999b, 2001).

This is the first study to provide comprehensive evidence of AED prescribing in youth in three European primary care settings. We are not aware of other published multinational population-based studies on AED prescribing in children and adolescents. We analyzed a large cohort comprising patients from the United Kingdom, Italy and The Netherlands, which allowed us to compare prescribing trends in different countries. The databases used are population-based and representative of the pediatric population in each country. In terms of limitations, the databases used only record prescriptions issued by a GP (in the United Kingdom and The Netherlands) or a primary care pediatrician (in Italy). They do not cover the patients who are only under specialist care such as residential epilepsy centers; therefore, the study may have underestimated the actual prevalence of AED prescribing. It needs to be noted that Italian pediatricians started contributing data to PEDIANET in

2000; this may explain the much smaller population in 2001 than in subsequent years. Consequently, it may lead to the slight overestimation of the prevalence of AED prescribing in Italy in 2001.

CONCLUSION

Conventional AEDs are still the main treatment choice for children with epilepsy, and the use of newer AEDs remains low in European countries. There is a considerable variation of newer AED use in children and adolescents among the countries, which may be attributable to different clinical guidelines and the healthcare systems within countries. The results of our study also highlight the lack of research capacity in conducting newer AED safety surveillance studies in young children with epilepsy using primary care data. Further research should explore the possibility of conducting a multinational AED safety study using a combination of large databases or secondary and tertiary settings to meet the research needs in children with epilepsy.

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