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Antiepileptic drug prescription in Dutch children from 2006–2014 using pharmacy-dispensing data

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ABSTRACT

Objective: In the last two decades several new antiepileptic drugs (AEDs) have become available. The aim of our study was to analyse whether and how AED prescribing patterns in Dutch children have changed during the last decade and whether these changes were supported by guidelines and results from recently available trials.

Methods: From a large community pharmacy-dispensing database in the Netherlands, we identified children aged 0–19 years who received at least one prescription for an AED between 2006 and 2014. Children who also received prescriptions for migraine or psychiatric disorders were excluded. We calculated year-prevalences and -incidences of AED use with emphasis on old versus new AEDs, and individual AEDs. We evaluated these results, including the course of AED prescribing.

Results: During the study period, the prescribing prevalence of old AEDs decreased from 1.61 per 1000 (95% C.I. 1.40–1.82) to 1.39 per 1000 (95% C.I. 1.18–1.60); for new AEDs it increased from 0.58 per 1000 (95% C.I. 0.45–0.71) to 1.35 per 1000 (95% C.I. 1.14–1.56). Valproic acid was the most frequently initiated AED in 2006. From 2010, prescribing of old and new AEDs became equal with levetiracetam as the most often initiated AED since 2012. This drug was recommended for all seizure types in the 2013 Dutch national epilepsy guideline. Only 5.5% of the children used AED combination therapy. Of those on monotherapy, 85.7% remained on the first prescribed AED.

Conclusions: In the last 10 years, prescribing of new AEDs increased at the expense of old AEDs. Levetiracetam has replaced valproic acid as the most frequently prescribed first line antiepileptic drug in children since 2012, which is in line with national guidelines.

1. Introduction

Epilepsy is one of the most common neurological disorders in childhood, with a median incidence of 82/100,000 in children and with antiepileptic drugs (AEDs) being first choice treatment (Kotsopoulos et al., 2002). During the last 25 years many new, so called second- and third-generation, AEDs have become available (Chung and Eiland, 2008) (Table 1). For most of them, no data from randomized controlled trials (RCTs) are available for children, especially not for AED monotherapy (Weijenberg et al., 2010). As a consequence, most of these new AEDs are only registered as add-on treatment for specific seizure types, and are prescribed off-label as monotherapy in children, not supported by evidence-based guidelines but based on the doctor's personal preference. Little is known about these individual and personal prescribing patterns and changes over time. Van de Vrie-Hoekstra et al. described utilization of AEDs of children in the Netherlands from 1997 to 2005 (van de Vrie-Hoekstra et al., 2008). Nine more studies have been published about prescribing patterns of AEDs in children, most of them describing cohorts before 2010 (Ackers et al., 2007; Hsia et al., 2010; Landmark et al., 2011; Cohen et al., 2012; Kwong et al., 2012; Nicholas et al., 2012; Dorks et al., 2013; Pickrell et al., 2014; Bourgeois et al., 2015). They all concluded that old AEDs (valproic acid, carbamazepine, phenytoin, phenobarbital) were most commonly prescribed, but that the proportion of prescribing new AEDs (lamotrigine, levetiracetam, topiramate, oxcarbazepine) was increasing considerably over time. Since 2010 new AEDs have become more established, more of them have become available, including liquid formulations for some, and new clinical trials and guidelines have been published (Freeman et al.,

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Table 1
Antiepileptic drugs in the Netherlands.

AED	Registration for children[a] in the Netherlands in 2018[b] (age; mono/add-on)	Year of registration in children[a] in Europe
Old		
Carbamazepine	all	n.d.
Clobazam	all	n.d.
Clonazepam	all	n.d.
Ethosuximide	all	n.d.
Phenobarbital	all	n.d.
Phenytoin	all	n.d.
Primidone	all	n.d.
Sulthiame	n.a.	n.a.
Valproic Acid	all	n.d.
New		
Felbamate	≥4 years add-on	1995
Gabapentin	≥12 years: mono ≥6 years: add-on	2007
Lacosamide	≥4 years mono and add-on	2017
Lamotrigine	≥12 years: mono ≥2 years: add-on	2000
Levetiracetam	> 16 years: mono > 1 month: add-on	2005
Oxcarbazepine	≥6 years mono and add-on	2000
Perampanel	≥12 years: add-on	2012
Pregabalin	n.a.	n.a.
Retigabine	n.a.	n.a
Rufinamide	≥4 years: add-on	2007
Stiripentol	all add-on	2007
Topiramate	≥6 years: mono ≥2 years: mono absence epilepsy ≥2 years: add-on	1999
Vigabatrin	West syndrome: mono all add-on	1998
Zonisamide	≥6 years: add-on	2013

AED: antiepileptic drug, n.a.: not approved in the Netherlands, n.d.: not documented.
[a] children < 16 years of age.
[b] College ter beoordeling van geneesmiddelen (2018).

2012; Glauser et al., 2010; Glauser et al., 2013; Majoie et al., 2016).

The aim of our study was to describe and analyse prescribing patterns of AEDs in children from 2006 to 2014. Furthermore, factors that may have influenced prescribing patterns are discussed, such as results of new RCTs, updates of (inter)national guidelines, off-label prescribing, costs, and/or personal experience of the prescribing doctors.

2. Material and methods

This study is an extension of an earlier study performed in our centre, and we used the same methodological principles (van de Vrie-Hoekstra et al., 2008). Information on drug use was extracted from the IADB.nl database (Visser et al., 2013). This database contains pharmacy-dispensing data of more than 600,000 persons from more than 50 Dutch community pharmacies located in different parts of The Netherlands, and is proven to be representative for the Netherlands with respect to age distribution and prevalence of drugs used (Visser et al., 2013). Community pharmacies contain an almost complete history of prescribed drugs because Dutch patients usually are registered at a single pharmacy. The IADB.nl database anonymously provides per patient, among other data, the information on drug use, like the dispensed drug represented in the Anatomical Therapeutical Chemical (ATC) classification, number of days the drug was prescribed, dispensing date, and the number of defined daily doses based on the definition by the WHO (Monster et al., 2002). In-hospital prescriptions and the use of over-the-counter drugs are not included in the database, but AEDs are non-over-the-counter drugs. Because data are stored anonymously and this database does not fall under the scope of the Medical Research Involving Human Subjects Act, approval of the medical ethics committee was not required.

2.1. Study population

Children aged 0–19 years who received at least one prescription for an AED between 2006 and 2014 were selected from the IADB.nl. All AEDs (ATC-group N03 A) available in the Netherlands were included, regardless whether they were registered for children. Furthermore, clobazam (ATC-code N05BA09) was included if used together with another AED, since this combination of drugs can be used for chronic treatment in children with epilepsy.

The IADB.nl provides information on drug use, without specification of the diagnosis. Since some AEDs are also prescribed for migraine or psychiatric disorders, we excluded children who were more likely to have migraine or a psychiatric disorder; i.e. children who received at least two or more prescriptions of propranolol and/or anti-migraine drugs (ATC-code N02C* or N07CA03), or received more than one prescription for an anti-depressant (ATC-code N06A*), or received more than one prescription for anti-psychotics (ATC-code N05A*) between 2006 and 2014. In the former Dutch study that used the same criteria, children who were more likely to have migraine or a psychiatric disorder were not excluded (van de Vrie-Hoekstra et al., 2008). In their study it was estimated that AEDs had been prescribed for epilepsy in at least 80% of the included children, while approximately 10% had received the drugs for mood disorders and 5% for migraine.

2.2. Data analysis

Prevalences and incidences of the use of all AEDs together were calculated per year over a period of 9 years from 2006 to 2014. AEDs were then stratified by type as old or new AED (Table 1) and prevalences and incidences were calculated, including 95% confidence intervals. Finally, prevalences and incidences were calculated for each individual AED. If no overlap between confidence intervals was observed, prescribing of AEDs was considered significantly different.

Annual prevalences were defined as the number of children receiving at least one prescription for an AED divided by the total number of children in the population (per sex and age category) in the respective years, and then multiplied by 1000.

The cumulative incidence of AED prescriptions was based on the number of children who received an initial prescription for a certain AED per year. Every child could be an initial user once, but when a child had two prescriptions for different AEDs as initial treatment, both AEDs were counted. To identify initial users, children had to be in the database at least 6 months before initial treatment with an AED started or were aged ≤2 years.

To evaluate the course of AED prescribing, children with a known start date and end date of therapy with AEDs were included as well as children having a running prescription at the end of the study period (31st of December 2014). The start of the therapy was defined the same way as for cumulative incidences. The theoretical end date of the treatment was calculated by dividing the prescribed number of tablets of the last prescription by the daily dosage. The therapy was defined as being ended if there were 90 days or more without AEDs after the theoretical end date of drug use. To be able to assess ending of AED use, children had to be in the IADB.nl for at least 90 days or more after the theoretical end date, otherwise they were excluded (except for children with a running prescription on 31st of December 2014). For each child, the start date and theoretical end date of each prescribed AED was calculated and, afterwards, children were divided in two groups: monotherapy or combination therapy. Combination therapy was defined as a prescription for two or more AEDs at the same time with an overlap of at least 90 days. Restart was defined as start after a discontinuation of AED treatment of at least 90 days. For all children, the course of AED prescriptions was evaluated.

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