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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 Therapeutic 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 N03A) 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.

Furthermore, the course of AED prescribing in our cohort was compared with national guidelines and results from available trials.

3. Results

From the IADB.nl, 2450 children were identified who received at least one prescription for an AED between 2006 and 2014. Of these 2450 children, 1280 (52.2%) were boys. Of the 2450 children 966 were excluded: 219 (9%) were supposed to have migraine, 720 (29%) were supposed to have a psychiatric problem and 27 (1%) only used clonazepam without another AED. Most of the children who were more likely to have migraine because they used propranolol and/or triptans, also used valproic acid and/or topiramate. Valproic acid was also one of the most often prescribed AED in children who most likely had a psychiatric disorder. Of the children considered to have a psychiatric problem, the minority used an anti-depressant (ATC code N06A*), amitriptyline being most prescribed, followed by selective serotonin reuptake inhibitors (SSRIs). The majority used an anti-psychotic drug (N05A*), or a combination of an anti-psychotic drug and an anti-depressant. Amitriptylin was often combined with pregabalin or gabapentin which suggests a diagnosis of neuropathic pain, whereas in combination with AEDs it is also prescribed for the treatment of chronic headache. Eventually, 1484 children were included in our study.

The estimated population of children covered by the IADB.nl per year, the annual prevalence, and cumulative incidence of AED use among these children are shown in Table 2. The overall prevalence and incidence remained constant and there were no differences between sexes.

3.1. Prescription of old versus new AEDs

Fig. 1 shows the overall annual prevalence of AED use, which varied from 1.95 to 2.45 per 1000 children, as well as the prevalence by type of AED (old versus new). Since clonazepam belongs to ATC-group N03A (old AED), clonazepam is also included in Fig. 1. From 2006 to 2011, old AEDs were significantly more often used than new AEDs as shown by the confidence intervals, but the use of new AEDs increased over the years at the expense of old AEDs. From 2012 onwards the prevalence of old and new AED use was identical.

3.2. Prescription of individual AEDs

All AEDs of ATC-group N03A were prescribed at some time to children in the IADB.nl database, except sulthiame and retigabine (not registered in the Netherlands). Fig. 2 shows the prevalence of AED use per year of the four most often prescribed AEDs and ethosuximide (prevalence of all individual AEDs are listed in supplementary Table 1). In 2006, valproic acid was by far most commonly prescribed. From 2009, the use of levetiracetam significantly increased at the expense of valproic acid and in 2012 the number of children using levetiracetam or valproic acid became more or less equal. The Dutch national epilepsy

guideline from 2013, which is based on the National Institute for Health and Care Excellence (NICE) guideline, expert opinions, critical evaluation of costs, and quality of the published trials, recommends levetiracetam for all seizure types in children and adults, also as monotherapy (Freeman et al., 2012; Majoie et al., 2016). Besides levetiracetam, carbamazepine and lamotrigine are first choice for focal seizures, and valproic acid and lamotrigine (without myoclonic seizures) for generalised seizures. The previous Dutch national guideline, published in 2006, recommended valproic acid and carbamazepine as first choice drugs for children < 12 years (van Donselaar et al., 2006).

Of the 1484 children, 835 (56.3%) started with AED treatment between 2006 and 2014 according to our definition of an initial user. Fig. 3 shows cumulative incidences of the four most often initiated AEDs and ethosuximide of these 835 users (cumulative incidences of all initiated AEDs are listed in supplementary Table 2). Although clonazepam was among the most initiated AEDs, it is not shown because it is usually not prescribed for long-term use, but as emergency treatment. The most remarkable, but anticipated, finding was the decrease of initial prescribing of valproic acid and increase of initial prescribing of levetiracetam after 2010 (Fig. 3). This overtake of valproic acid by levetiracetam was first seen in the cumulative incidences, because these represent the start of a new prescription. Since prevalence represents all prescriptions, the overtake by levetiracetam occurs only later in the prevalence figures. For the remaining AEDs the cumulative incidences remained constant and were below 0.15 per 1000 children (supplementary Table 2). The incidence of ethosuximide was zero during many years, but from 2013 onwards it has been prescribed more frequently (Fig. 3). In 2010, ethosuximide was shown to be relatively most effective and best tolerated in children with childhood absence epilepsy, compared to valproic acid and lamotrigine (Glauser et al., 2010). This has led to adjustments of various guidelines, both national and international.

3.3. Evaluation of the course of the therapy

In 474 (56.8%) of the 835 initial users, the course of AED prescribing with respect to monotherapy and combination therapy could be evaluated (Fig. 4). The other 361 children were censored because the child was less than 90 days in the IADB.nl after the end of the treatment or the child left the database with a running prescription before 31st of December 2014. Only 26 children (5.5%) used combination therapy with an overlap of at least 90 days of two or more different AEDs; the other 448 children only had monotherapy.

The most frequent initially prescribed AED for monotherapy was valproic acid (34.2%) followed by levetiracetam (14.1%) and carbamazepine (11.6%).

Forty-two of the 395 children who used only one single AED restarted treatment with an AED after having been without AEDs for at least 6 months, most likely because of seizure recurrence; 31 (73.8%) of these children started with the same AED as they previously used.

Forty children switched from one AED to another, most likely

Table 2

Population of the IADB.nl, prevalence and incidence of AED use per 1000 children (0–19 years).

Year	Total number of children	Prevalence	95% Confidence interval	% male	Incidence	95% Confidence interval	% male
2006	135,428	1.99	1.76–2.23	53	0.50	0.38–0.62	51
2007	135,745	2.11	1.87–2.36	53	0.63	0.50–0.77	60
2008	134,328	1.95	1.71–2.19	51	0.52	0.40–0.64	51
2009	136,444	2.44	2.18–2.70	54	0.79	0.64–0.94	59
2010	138,212	2.17	1.92–2.41	57	0.55	0.43–0.67	54
2011	135,410	2.45	2.19–2.71	52	0.89	0.73–1.05	47
2012	133,447	2.44	2.18–2.71	57	0.87	0.72–1.03	55
2013	130,458	2.40	2.14–2.67	52	0.83	0.67–0.98	47
2014	119,707 ^a	2.32	2.05–2.59	52	0.68	0.53–0.82	55

^a decrease in population because of drop-out of one pharmacist.

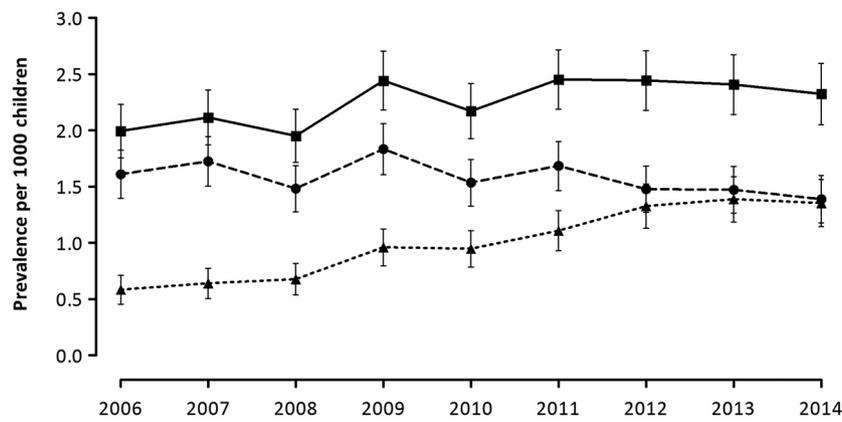


Fig. 1. Prevalence (including confidence intervals) of all, old and new AED use per 1000 children (aged 0–19 years) per year. Prevalence of all AEDs is less than old AEDs plus new AEDs, since children could have a prescription for an old and new AED at the same time. ■ = all AEDs, ● = old AEDs, ▲ = new AEDs.

because of inefficacy or adverse effects, which took place within 2–3 months in most children, titration schedules included.

In 13 children treatment regimen was unclear or they received two prescriptions for an AED at the same moment, but only for a very short period (< 1 month).

Regarding combination therapy, 22 of the 26 children on combination therapy started with monotherapy, 14 of them with valproic acid. Most children switched from monotherapy to combination therapy within one year. Valproic acid and levetiracetam or valproic acid and lamotrigine were most commonly prescribed as combination therapy, followed by combinations with carbamazepine and ethosuximide.

4. Discussion

Our study of AED utilization in an unselected paediatric cohort from 2006 to 2014 shows a significant increase of prescribing of new AEDs at the expense of old AEDs, with the strongest effect for levetiracetam versus valproic acid. The overall prevalence and incidence remained constant over the years despite increased possibilities of non-medical treatment such as epilepsy surgery, vagal nerve stimulation and ketogenic diet (Aaberg et al., 2018).

The annual prevalence of AED use in our study is comparable with the findings of Hsia et al. (Hsia et al., 2010), who also used data from the Dutch population. They included databases in which the diagnosis was stated, which allowed them to study children with epilepsy only. The prevalence of AED use in our study was, however, almost half of

the prevalence observed by van de Vrie et al. (van de Vrie-Hoekstra et al., 2008). They estimated that AEDs had been prescribed in 10% of the children for mood disorders and in 5% for migraine, but these patients were included in the analyses. Using the same exclusion criteria as van de Vrie-Hoekstra, we excluded 939 (38%) children with prescriptions more likely to be for migraine or psychiatric- or mood disorders, although some of them might also have had epilepsy. Based on this evaluation, we think that children were correctly in- or excluded in our study.

The incidence of initiating an AED was highest during the first year of life (data not shown), which is in line with the peak of first seizures in children at that age (Hauser et al., 1993; Aaberg et al., 2017).

4.1. Prescription of old versus new AEDs

An increase of prescribing of new AEDs at the expense of old AEDs was expected from previous studies (Ackers et al., 2007; van de Vrie-Hoekstra et al., 2008; Hsia et al., 2010; Landmark et al., 2011; Cohen et al., 2012; Kwong et al., 2012; Nicholas et al., 2012; Dorcks et al., 2013; Pickrell et al., 2014; Bourgeois et al., 2015), but was not yet observed in cohorts from before 2010. Cho et al. described an overtake of old AEDs (mainly valproic acid) by new AEDs (mainly oxcarbazepine) as first choice AED in children with different seizure types in a tertiary children’s hospital between 2001 and 2012 (Cho et al., 2015). In 2014, old AEDs were still first choice in 87.5% of 694 children derived from seven specialized clinics for management of epilepsy in Jordan (Albsoul-Younes et al., 2016). According to the authors this

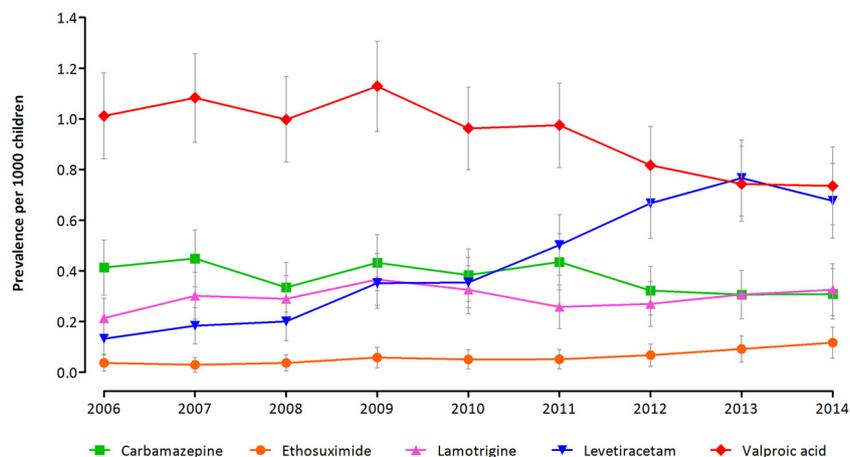


Fig. 2. Prevalence of individual AED use. Prevalence (including 95% confidence intervals) of individual AED use per 1000 children (aged 0–19 years) per year of the four most often prescribed AEDs and ethosuximide.

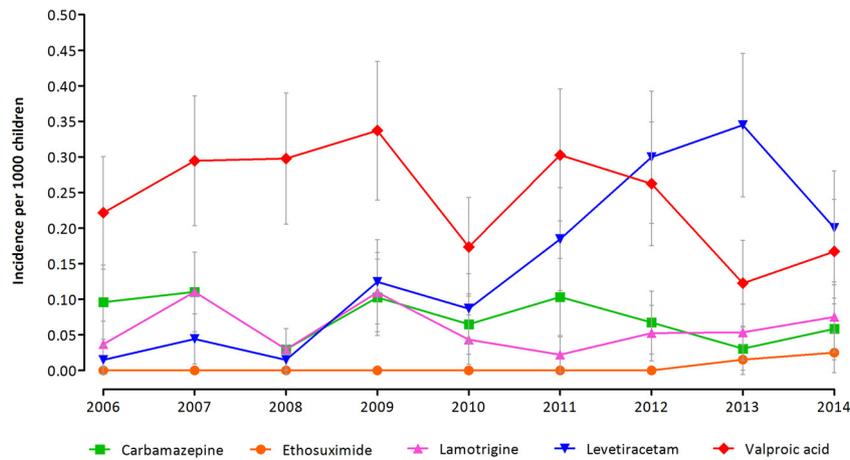


Fig. 3. Cumulative incidences of individual AED use. Cumulative incidences (including 95% confidence intervals) of individual AED use per 1000 children (aged 0–19 years) per year of the four most often initiated AEDs and ethosuximide.

might be due to the conservative attitude of clinicians in their country when treating younger children (mean age of children in this study was 8.6 years).

4.2. Prescription of individual AEDs and current evidence

Our study showed that from 2012 onwards levetiracetam has replaced valproic acid as the most frequently prescribed first line AED in children, at least in the Netherlands. Since the introduction of levetiracetam, a linear increase of the use of levetiracetam was seen in the UK, Australia and Hong Kong, but levetiracetam did not exceed lamotrigine until 2010 (Ackers et al., 2007; Cohen et al., 2012; Kwong et al., 2012; Pickrell et al., 2014). The evidence for levetiracetam monotherapy in children is still very limited with only level D evidence (potentially efficacious or effective) in children with benign epilepsy with centrotemporal spikes (Glauser et al., 2013), but levetiracetam is recommended for all seizure types in the Netherlands, also as monotherapy (Majoie et al., 2016). Remarkably, levetiracetam was already the most frequently prescribed AED before it was recommended in the

Dutch national guideline of 2013. Apart from the effectiveness and safety profile of levetiracetam, the availability of a generic formulation since 2011 could have played a role in the increase (Weijenberg et al., 2015). In the NICE guideline, that takes economic aspects into account, levetiracetam is only recommended as first-line monotherapy treatment for focal or myoclonic seizures if other first-line drugs are unsuitable or not tolerated (Freeman et al., 2012). Costs are less important or not taken into account in the other guidelines.

The significant decrease in prevalence and incidence of valproic acid use was independent from sex (data not shown), whereas a stronger decrease in girls could be expected because of its teratogenicity (Tomson et al., 2015, 2016).

We were not able to confirm the position of lamotrigine as the most often prescribed new drug as reported by others (Ackers et al., 2007; van de Vrie-Hoekstra et al., 2008; Hsia et al., 2010; Landmark et al., 2011; Cohen et al., 2012; Nicholas et al., 2012; Dorcks et al., 2013; Pickrell et al., 2014). Data from the Standard And New Antiepileptic Drugs (SANAD) study from 2007, which included adults and children aged > 4 years, showed that lamotrigine is clinically better than

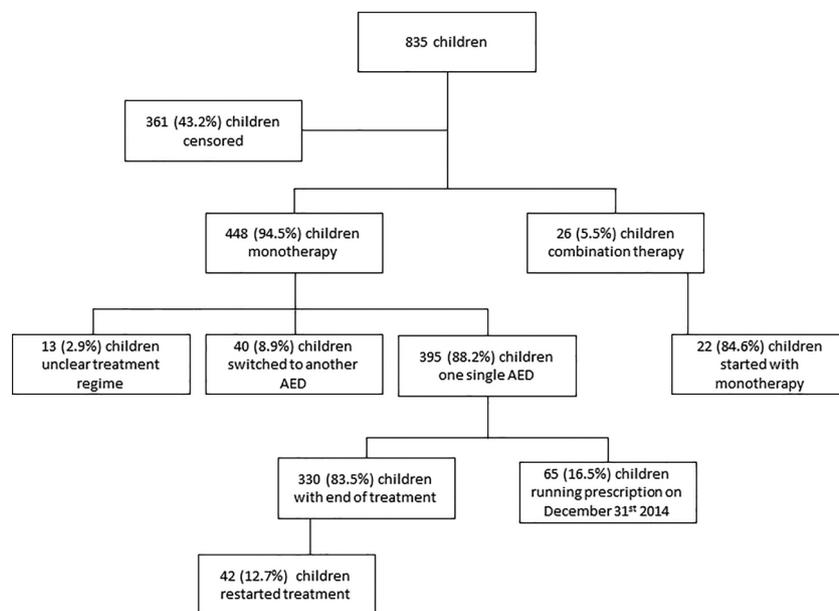


Fig. 4. Flowchart of AED prescribing in our cohort. 361 children were censored because the child was less than 90 days in the IADB.nl after the end of the treatment or the child left the database with a running prescription before 31st of December 2014.

carbamazepine in focal epilepsy (Marson et al., 2007a, b). Preference for lamotrigine over carbamazepine was also observed in three population-based studies that included children until 2009 or 2010 (Cohen et al., 2012; Kwong et al., 2012; Pickrell et al., 2014). Although lamotrigine is recommended for all seizure types in children and adults in the Dutch guideline, our study shows that its prescription was significantly lower than of levetiracetam from 2012 onwards, and did not change significantly over time. Its slow titration schedule, to prevent a skin rash, could be an explanation for this.

In general, evidence of efficacy (seizure freedom) and effectiveness (patient retention) of AEDs as initial monotherapy for epileptic seizures and syndromes is very limited in children; strong evidence from RCTs only exists since 1997 for oxcarbazepine in children with focal seizures and since 2010 for ethosuximide and valproic acid in children with absence seizures (Guerreiro et al., 1997; Glauser et al., 2010; Glauser et al., 2013). Still, only a few studies reported an increase of prescribing of oxcarbazepine, whereas other new AEDs (without sound evidence of efficacy and safety) were more often prescribed (Landmark et al., 2011; Dorks et al., 2013; Bourgeois et al., 2015). Only in the study of Cho et al. oxcarbazepine was the most commonly prescribed AED (Cho et al., 2015).

We found a small but linear increase in the prescription of ethosuximide in our cohort after 2010 (Figs. 2 and 3), most likely due to the publication of the study of Glauser et al. in children with childhood absence epilepsy (Glauser et al., 2010). This was not observed in the only other study that included children after 2010 (Cho et al., 2015).

Performing RCTs in children is quite complex, especially when an RCT is investigator-initiated (Weijenberg et al., 2017). Guidelines for treatment of children with epilepsy are therefore often based on expert opinions together with some evidence from a few well performed RCTs (Marson et al., 2007a, b; Glauser et al., 2010; Weijenberg et al., 2010; Glauser et al., 2013). In clinical practice this results in prescribing new AEDs off-label (Borges et al., 2013). The influence of costs on AED prescribing in children is uncertain, since new AEDs are prescribed in children a few years after their registration for adults and therefore closer to or even after the patent expiring date, consequently lowering its price. Last, but not least, the role of personal preferences of the local (epilepsy) specialist for certain AEDs should not be underestimated (Appleton et al., 2012).

4.3. Limitations

We describe utilization patterns of AEDs in children based on pharmacy-dispensing data from the IADB.nl; a database proven representative for the Netherlands. However, the database does not contain information about diagnosis or indication for prescription. We tried to exclude children more likely to receive AEDs for migraine and/or a psychiatric disorder as accurately as possible. However, probably this has led to the exclusion of some patients with both epilepsy and migraine or a psychiatric disorder.

Another limitation of our study is that the evaluation of the prescribing patterns of AEDs in children is based on dispensing instead of actual drug use and could only be done in 474 (56.8%) children due to our strict inclusion criteria. However, we calculated the use of AEDs in person-days, which is much more accurate than calculating person-months as done in other studies (van de Vrie-Hoekstra et al., 2008; Landmark et al., 2011). Moreover, it gives the opportunity to define combination therapy as a prescription for two or more AEDs at the same time with an overlap of at least 90 days. This definition represents combination therapy better; otherwise, it could also indicate a switch from one AED to another AED with a short overlap.

5. Conclusion

Our study shows a stable overall utilization of AEDs in the last decade together with a significant increase of prescribing of new AEDs

at the expense of old AEDs. The most pronounced change was seen for levetiracetam replacing valproic acid as the most frequently prescribed first line antiepileptic drug in children since 2012, even though current evidence of its efficacy and safety is limited and it is still prescribed off-label as monotherapy. An expected increase of prescribing of lamotrigine was not found. Apparently, personal preferences of the local (epilepsy) specialist for certain AEDs probably play an important role in prescribing AEDs in children.

Author contributions

A. Weijenberg: design and conceptualization of the study; data collection, analysis, and interpretation; and writing the manuscript

J.H.J. Bos: conceptualization of the study; data collection and analysis; and revising the manuscript.

C.C.M. Schuling-Veninga: conceptualization of the study; data interpretation; and revising the manuscript.

O.F. Brouwer: design and conceptualization of the study; data interpretation; and revising the manuscript for intellectual content

P.M.C. Callenbach: design and conceptualization of the study; data interpretation; and revising the manuscript for intellectual content

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Amerins Weijenberg: no conflicts of interest

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.eplepsyres.2018.07.011>.

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