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Trends in sodium valproate prescriptions among children aged 0 to 14 years between 2010 and 2016: A study based on the French National Health Insurance Database.

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Highlights:

- Since 2010, initiations of VPA have decreased among girls aged 0 to 14 years.
- Initiations of LTG and LEV increased among girls over the study period.
- In 2016, GPs were still initiating VPA among girls aged 11-14 years.
- GPs remain the primary healthcare professionals for epileptic patients.

Abbreviations:

AED	Antiepileptic drugs
ANSM	Agence Nationale de Sécurité des Médicaments des produits de santé (French agency for the safety of medicines and health products)
ATC	Anatomical Therapeutic Chemical
CCAM	Classification Commune des Actes Médicaux
CIP	Code identification produit (national registration code)
CMUc	Couverture médicale universelle complémentaire (Complementary Universal Health Insurance)
DCIR	Données de Consommation Inter-Régimes (Health reimbursement database)
DP	Diagnostic principal (main diagnose)
DR	Diagnostic relié (related diagnose)
DAS	Diagnostic associé significatif (significant related diagnose)
EEG	Electroencephalogram
EMA	European Medicines Agency
GP	General practitioner
ICD	International Classification of Diseases
LEV	Levetiracetam
LTI	Long-Term Illness
LTG	Lamotrigine
PMSI	Programme de Médicalisation du système d'information (French hospital discharge database)
PY	Person-Year
SNIIRAM	Système National d'Information Inter-Régimes de l'Assurance Maladie (French National Health Insurance Database)
VPA	Sodium valproate

1) Introduction

Epilepsy is one of the commonest serious chronic neurological disorders. Worldwide there are at least 65 million people living with epilepsy. The incidence of epilepsy in the infantile period is high, with an estimation of about 70 per 100,000 inhabitants in European countries. [1]

The management of epilepsy among children is different from that among adults because of a broader spectrum of syndromes in children and because evidence on the effectiveness of antiepileptic drugs (AEDs) is not always established. [2–4] A therapeutic choice must still be made even if a precise diagnosis is not straightforward at the onset of epilepsy.

In the 2000s, new AEDs arrived on the drug market and changed practices in the treatment of epilepsy for both children and adults. [5,6] The changes could also be related to an awareness of the risks associated with in utero exposure to earlier antiepileptic drugs, such as sodium valproate (VPA), which has been integrated into clinicians' practices, especially neurologists, as demonstrated in Europe and across the Atlantic. [7–9] In 2014, as recommended by the European Medicines Agency (EMA), the French Agency for the safety of medicines and health products (ANSM) initiated a communication strategy with a "Dear Doctor" letter [10] to remind healthcare professionals of the teratogenic effects of VPA (major congenital malformations [11], neuro-developmental delays [12], autism spectrum disorders [13,14]). A few months later, in May 2015, French clinicians were also informed that the conditions for prescription and issue of VPA and its derivatives would be reinforced. [15] Since the 1st of January 2016, VPA and its derivatives should, whenever it is possible, not be prescribed to women of childbearing age, except in case of intolerance or ineffectiveness of alternatives. Nonetheless, the unchallenged efficacy of VPA, with its broad spectrum of activity, makes it a drug of choice for the first-line treatment of epilepsy.[16] More recently in Europe, likewise,

VPA has been contraindicated for women of reproductive potential, except in case of intolerance or ineffectiveness of alternatives.

We aimed to evaluate trends in AED prescriptions, especially in the period 2015-2016, to tailor a communication strategy, focusing on young epileptic girls, for whom VPA should not be chosen as the first-line treatment.

1) Methods

We conducted a nationwide study using the French National Health Insurance Database (SNIIRAM), over 7 years (2010-2016), to describe the trends in VPA prescription among epileptic girls 0 to 14 years of age, particularly as first-line treatment, and we compared this with prescribing trends for boys aged 0 to 14 years.

Source

SNIIRAM anonymously and comprehensively links a health reimbursement database (DCIR) to the French hospital discharge database (PMSI). The DCIR contains i) demographic data such as date of birth, gender and information on complementary insurance systems or the presence of CMUc (Couverture médicale universelle complémentaire) (Complementary Universal Health Insurance), an insurance cover for low-income status individuals ii) medication, recorded as dispensed packs, including a single national registration code (CIP), and Anatomical Therapeutic Chemical (ATC) code is also provided with the date of prescription, the profession of the prescriber and date of issue iii) the presence of long-term illness (LTI) status and date of first registration of chronic illness status, which gives registered patients full coverage for all medical expenses related to the illness. PMSI covers all overnight or day hospitalizations in the public and private sectors, and includes short-term stays in medical, surgical or obstetric facilities. It collects information on the patients and their diagnoses (primary diagnoses (DP—diagnostic principal /DR—diagnostic relié) (main and related diagnoses)) and comorbidities or complications (DAS—Diagnostic associé significatif) (significant related diagnoses) using ICD10 codes (International Classification of Diseases, 10th revision), surgical/interventional procedures (CCAM–Classification Commune des Actes Médicaux) and prescription of particularly expensive drugs.

The SNIIRAM database was developed to ensure the reimbursement of individual medical claims but was not intended to serve medical research. It does not comprise any clinical information concerning results related to consultations, prescriptions or examinations. Using it to follow individual patients over time and across different data sets can therefore be challenging.

It has previously been used to describe prescription trends with respect to recommendations [17] in the context of epilepsy management [18] and VPA exposure [19].

Patient selection

All patients aged 0 to 14 years with at least one issue of antiepileptic drug (AED) recorded between 2010 and 2016 were selected. An AED was defined as a drug licensed for the treatment of epilepsy in France, i.e. drugs listed under the ATC code N03A, plus two benzodiazepines, diazepam (N05BA01) and clobazam (N05BA09). As diazepam is mainly authorized for febrile convulsions, patients who were prescribed diazepam only were excluded. Patients, who were prescribed sodium divalproex (N03AG01) or valpromide (N03AG02) were also excluded because these medications are mostly indicated in psychiatric setting.

Data collection

For descriptive purposes different patient characteristics were collected: date of birth to determine the age at the beginning of the study (January 1st, 2010), gender, LTI status, CMUc status, which provides information on patient socio-economic level. Prescription characteristics were obviously studied: date of prescription, date of issue, drug issued, number of boxes and also information on the prescriber, as working in a healthcare facility or in the community.

Statistical analysis

For each patient matching the selection criteria and for each prescription we determined whether it was a prevalent or an incident use (first delivery after birth or after one year without AED issue). A one-year history was necessary to obtain this information and this is the reason why we retrospectively collected data up to 2009. We also determined which AEDs were prescribed (grouping them by ATC7 Code). The number of different ATC7 codes prescribed defined the polytherapy criterion.

For each year, we first calculated the percentage of VPA and that of each ATC7 code other than VPA among incident uses, and plotted these proportions by gender and age category. We use the following age categories: 0-2 years, 3-6 years, 7-10 years and 11-14 years. For purposes of comparison, we calculated the relative reduction in prescriptions between the percentage of VPA prescribed in 2010-2014 and the one in 2016. We intentionally excluded the year 2015, during which time the EMA and ANSM promoted a huge campaign to avoid the use of VPA among women of childbearing age. The impact of the 2015 risk minimization measure was likely to be more obvious in 2016, the year we chose for comparison.

We then calculated the incidence rate of VPA prescription among prevalent uses of any other AEDs and plotted them by gender and age category: the number of VPA initiations was divided by the number of person-years (PY) with a prevalent use of another AED. The types of AED before VPA initiation were described.

Finally we calculated the incidence rate for VPA discontinuations among prevalent users of VPA and the proportion for each ATC7 code among AED prescriptions after VPA discontinuation. VPA discontinuation was defined by the last VPA delivery date followed by at least one year without VPA issue, assuming one year of follow-up was available.

Statistical analyses were performed using SAS 9.4 (SAS INSTITUTE, North Carolina, USA) via SAS Enterprise Guide®.

Regulatory approval

The study was granted regulatory approval as part of a larger program on VPA exposure (CNIL 03/11/2016). The study was conducted with direct access to the SNIIRAM database under ANSM agreement.

2) Results

General characteristics of the study population

In the SNIIRAM database, 113,362 children fulfilled the selection criteria, 61,259 boys and 52,103 girls. Almost all patient characteristics were similar between boys and girls (Table 1). The number of incident uses over the study period (seven years) was 93,557: 42,493 among girls and 50,064 among boys. The median age at the beginning of the study was five years.

The most frequently prescribed antiepileptic drugs were, in decreasing order: sodium valproate, largely predominant, followed by diazepam, lamotrigine (LTG), levetiracetam (LEV), clobazam and clonazepam. Most of the drugs were prescribed in monotherapy.

Prescribing trends for sodium valproate

Figure 1 shows the trends in VPA initiations over the study period by gender and age category. Focusing on children aged 0-10 years and incident uses only in 2010, the proportion of VPA prescriptions ranged between 40 and 50%, without a clear gap between boys (nearly 30%) and girls (20%). Globally, the proportion remained quite stable until 2014 and then decreased. In 2016, the proportion of VPA still accounted for 11% of AED initiations among girls aged 11-14 years.

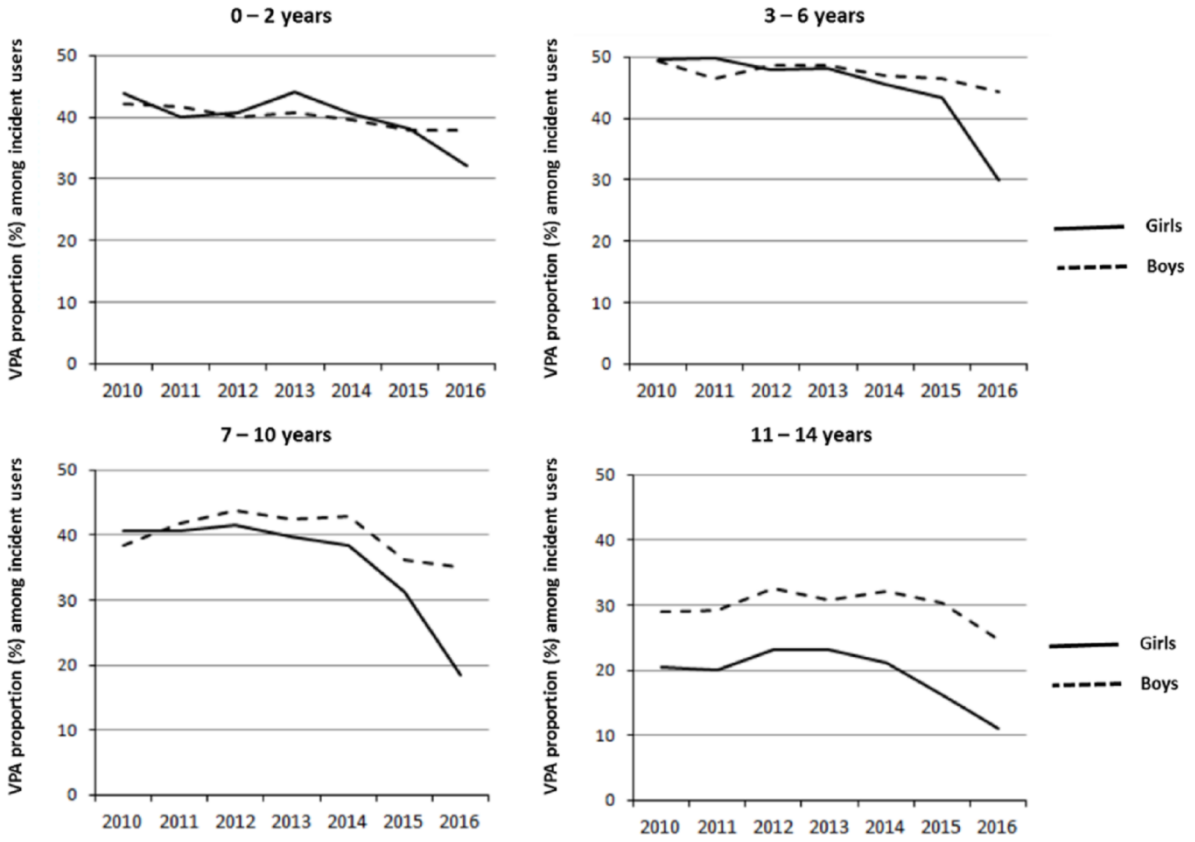


Figure 1. Trends in sodium valproate initiations over the study period by gender and age category. *(2-column fitting image)*

Between 2010 and 2016, the proportions of prescriptions for LEV, LTG, ethosuximide, gabapentin in incident use increased among girls aged 0-14 years (Figure 2).

Table 2 reports the proportion of VPA among AED initiations according to prescriber category. In 2010, initiation of VPA among girls by specialists (including hospital practitioner and neurologist or pediatrician working in community) was relatively frequent (over 40%). This frequency was lower in 2016 for neurologists (-24.5% between 2010 and 2016), hospital practitioners (-20.6%) and pediatricians (-15.6%). In contrast, the frequency of VPA use among AED initiations by General Practitioners (GPs) was relatively stable over the period, at around 20-25%.

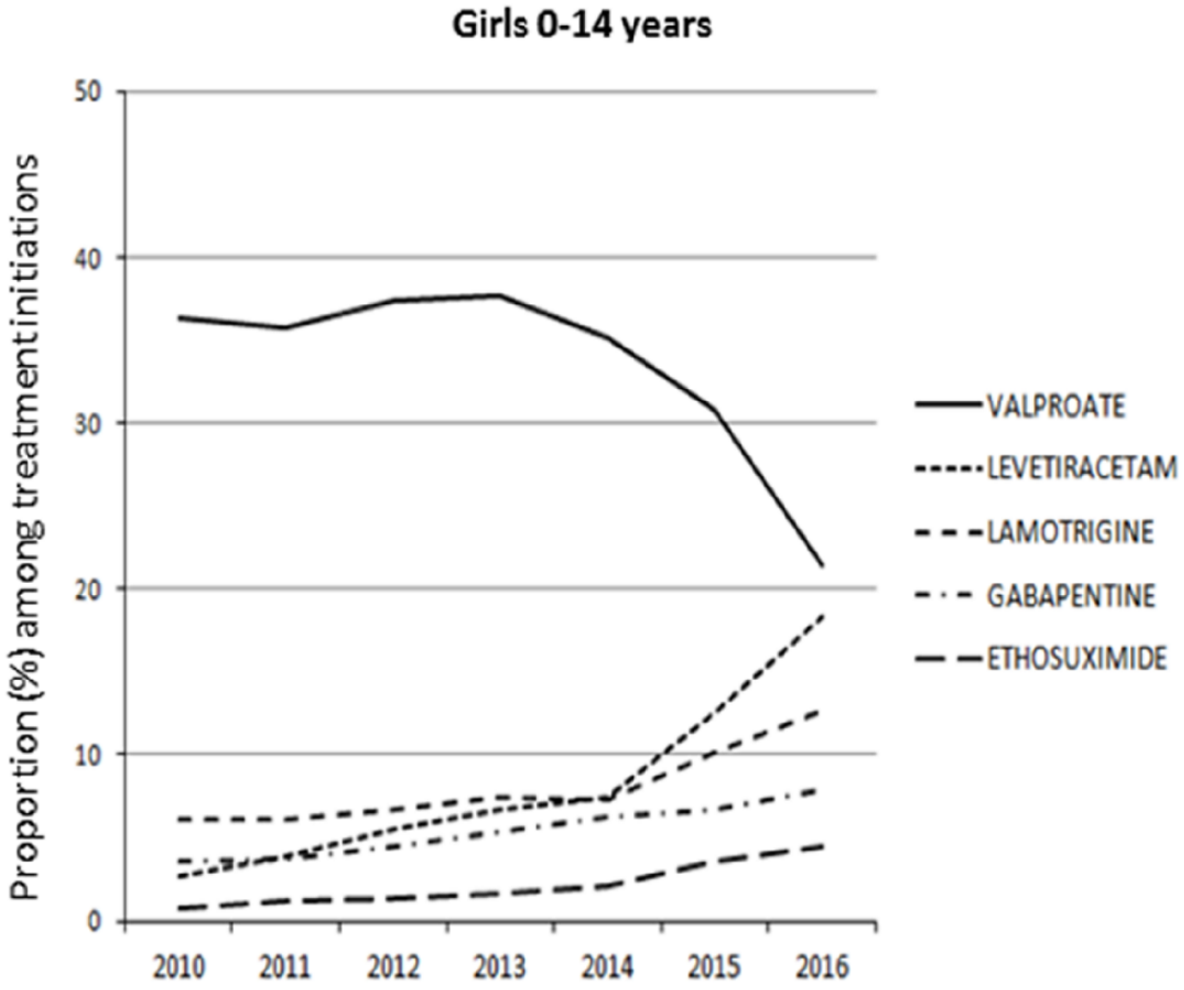


Figure 2. Trends in antiepileptic treatment initiations over the study period among girls aged 0-14 years. *(1-column fitting image)*

Figure 3 shows trends in initiating VPA (add-on or switch) among prevalent users of any AED other than VPA over the study period by gender and age category. The number of PY treated with an AED other than VPA was around 5000 per year over the study period. In this population, the incidence rate for VPA prescription decreased from 18.3 in 2010 to 9.7 per 100 PY in 2016 for girls (47% relative reduction) versus 20.3 to 16.1 per 1000 PY for boys (relative reduction of 21%). These relative reductions were homogeneous across the different age groups.

It can be noted that the incidence rate for VPA prescription among teenage girls (11-14 years of age) and young girls (7-10 years of age) was relatively low over the study period (less than 10 for 100 PY). The most frequently prescribed AEDs just before VPA initiation were benzodiazepines, lamotrigine and vigabatrine, mostly in monotherapy (91% in 2010; 89% in 2015).

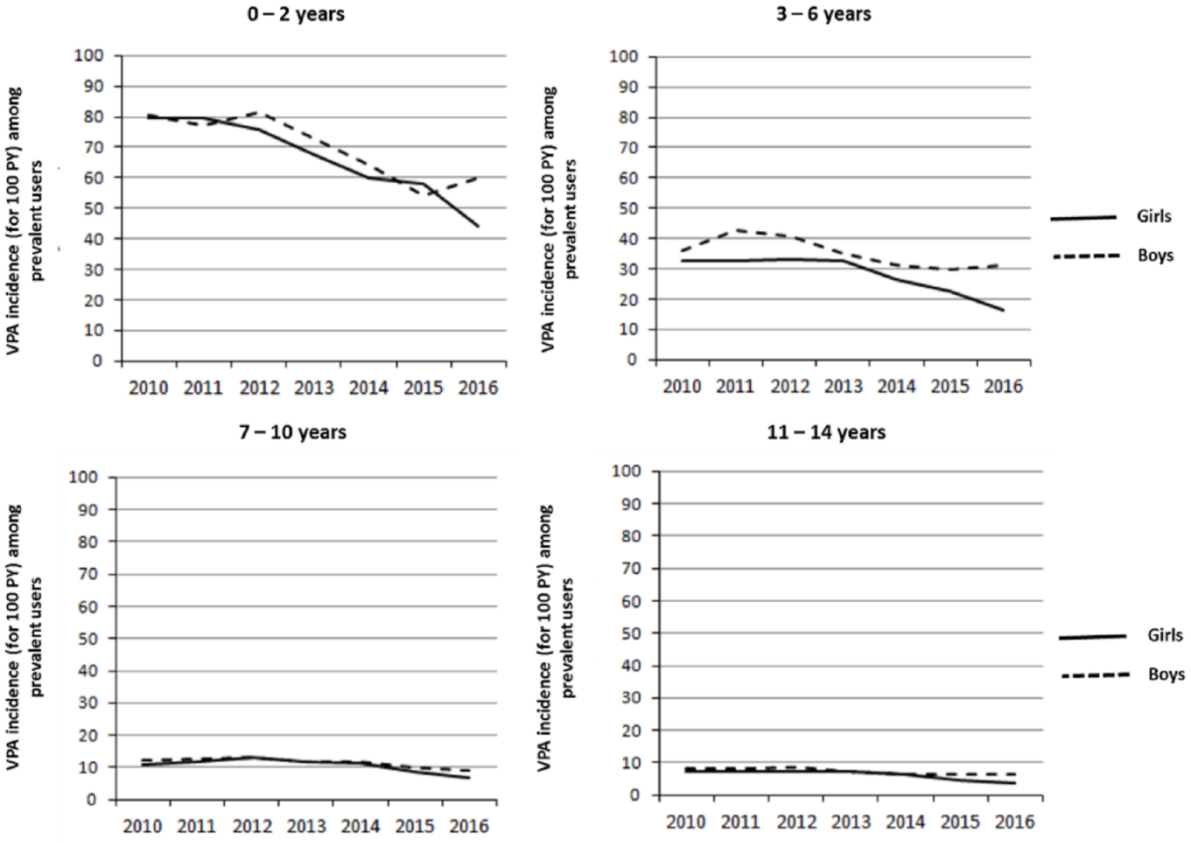


Figure 3. Trends in sodium valproate initiations (add-on or switch) among children already treated with another antiepileptic drug over the study period, by gender and age category. *(2-column fitting image)*

Discontinuation of VPA was defined as an issue of VPA that was not followed later in the year by another issue of VPA, assuming one year of follow-up was available. Discontinuation of VPA was quite high (around 35 per 100 child-years) but quite stable over the study period and similar in girls and in boys. It was higher among young children (0-6 years old) than among older children (7-14 years old) (40 to 60 per 100 PY versus 30 per 100 PY).

In around 70% of cases, VPA discontinuation was not followed by another AED. Before withdrawal of sodium valproate treatment, the antiepileptic treatment duration was for the majority 1 year or more (60%), while in 18% of cases it was less than 1 month (only 1 issue). It was different among children aged 0-2 years, for whom only 1 month of antiepileptic treatment before VPA withdrawal was observed in 30% of cases.

The remaining 30% “switched” from VPA to another AED, mostly in monotherapy. Lamotrigine and levetiracetam were the most frequently prescribed AEDs.

Discussion

Our study evaluating the trends in sodium valproate (VPA) prescription among children highlighted a number of points.

Firstly, the proportion of VPA prescriptions among incident uses of antiepileptic drugs decreased in both genders over the study period, but more so among girls, especially in teenage girls. Over the 1993 to 2006 period, the prevalence of VPA per 1000 prescriptions among females (12-18 years old) significantly decreased from 0.94 (95% CI 0.80 to 1.09) to 0.63 (95% CI 0.55 to 0.72). [7]. Over the 2000 to 2010 period, girls were prescribed sodium valproate significantly less often as a first-line AED (74% versus 46%). [20] Our study enables these observations to be updated and it points to a substantial decrease in VPA use among teenage girls, possibly as a result of new information released in the media on its teratogenic effects. [10]

Secondly, the alternatives to VPA, for which frequencies increased during the study period, were mainly levetiracetam, then lamotrigine, followed by ethosuximide and gabapentin. Increases were always more pronounced for girls than for boys. Changes in the choice of the first AED for a new onset of epilepsy are similar to those observed in previous years in other European countries. [7,9,20] During the 2000s, it was established that the use of first-generation AEDs (VPA, carbamazepine, phenytoin, phenobarbital) decreased over time, at least in developed countries, concomitantly with the arrival of new AEDs on the market. [5,9,21,22] More recently, a trend towards more LEV and LTG prescriptions could also be explained by prescribers' knowledge of the significantly lower rates of major congenital malformations for these drugs. [11]

Thirdly, the proportion of VPA initiations among girls already under treatment greatly decreased for specialists but remained stable over the study period for GPs. The proportions of AED prescriptions by three different prescriber categories (GPs, specialists, psychiatrists) were studied by Hollingworth & al. in Australia over a 5-year period (2002-2007). They observed an increase in prescribing of new AEDs, such as levetiracetam, topiramate and lamotrigine, by GPs. Also, the proportion of prescriptions by GPs was the highest for phenytoin, followed by sodium valproate. [23] Prescriber data in this study indicated a shift from specialist to GP prescribing. Neurologists commonly initiate AED prescription for epilepsy and the subsequent prescribing is usually taken on by GPs. This pattern should be applied in France according to the latest recommendations. Nevertheless, VPA accounted for 20% of AEDs initiated by a GP. In the clinical context of epilepsy, primary care should lead to an initiation of antiepileptic treatment to limit possible seizures and should not have to be delayed until the final therapeutic choice made by a specialist. Continuing prescription of VPA as first-line treatment by GPs could reflect difficulties in healthcare trajectories for the French epileptic population, with difficult access to specialized care (EEG, neurologist, tertiary care hospitals), compelling GPs to ensure the care of first seizures with VPA, on the grounds that this AED has a broad spectrum of activity.

Finally, discontinuation of VPA was stable over the study period, among girls but also among boys, and did not seem to be influenced by the recommendations. In 70% of cases, the withdrawal of VPA was not followed by another AED, and this was all the more true among children aged 0-2 years. The exact reasons why treatments were discontinued is not known, but some situations can justify it. For instance, treatment with VPA can be discontinued after a diagnosis of recovery. VPA is the drug of choice for many epileptic syndromes, and widely prescribed by GPs. After specialist consultation or access to electroencephalogram (EEG), a

diagnosis other than epilepsy can be made. An antiepileptic treatment can also be prescribed on a temporary basis, for example in case of accidental seizure after meningitis, head trauma, or febrile seizures. In these cases, the treatment duration is short (a few months) and pursuit of antiepileptic treatment is not expected. Among older children, discontinuation of the antiepileptic treatment can occur in certain types of syndrome (childhood absence epilepsy, benign rolandic epilepsy) after a seizure-free period, or to limit the neurocognitive impact of AEDs. Prolonged discontinuations do not systematically lead to seizure recurrence and are possible for some patients. [30, 31]

Compared to previous studies, our investigation, by using a large population database over a recent period of time, is the first one that evaluates latest trends in prescribing valproate focusing on children.

A first limitation is the definition of incident use, which could include a re-instatement of treatment, as it was based on a one-year AED-free period only. However, recommendations on VPA use encompass AED initiation as well as resumption of treatment. A second limitation is the fact that the SNIIRAM database does not enable the pathological context of prescriptions to be identified because no clinical data is available except for the hospital discharge diagnoses.. Nevertheless, we believe that AEDs are primarily prescribed in children for anticonvulsant purposes and, more importantly, our objective was to observe a decrease in valproate prescribing trends regardless of indication. Finally, patients in long-term facilities were not included in this study because AED issues for these patients were not available in the database. These patients often have pharmaco-resistant epilepsy, or at least epilepsy that is hard to stabilize with different AED prescription strategies. [23, 24]

Conclusion

~~To the best of our knowledge, this is the first study describing VPA and alternative prescription patterns in a large pediatric population over a long period of time taking into account the new French recommendations concerning VPA use.~~ This large-scale study describes changes in paediatric prescription patterns following the implementation of a national information campaign on the appropriate use of VPA.

The observed trend was as expected, with a decrease in VPA initiations, especially after 2015, among children whether or not already treated with an AED. This decrease was observed in both genders, more pronounced for girls, and sharper in 2016. The proportion of VPA prescriptions among the different AED prescriptions decreased between 2010 and 2016 in favor of LTG and LEV, often used as monotherapy. Whatever the nature of the prescription (initiation or not), they came mainly from hospital prescribers (specialists) and from neurologists or pediatricians.

All prescribers reduced VPA prescriptions between 2010 and 2016, especially the neurologists. VPA initiation remained stable among GPs. In 2016, the Prescription and Drug Supply Conditions changed for VPA in France: it is now mandatory for it to be initiated by a specialist. Furthermore, the European Medicines Agency recently changed the recommendations for VPA use: it should not be prescribed to women of childbearing potential except if there is no other treatment option, and provided the woman is on adequate contraception. Further evaluations in 2016, 2017 and 2018 could be valuable.

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Table 1: Characteristics of the study population.

	Girls (N=52103)	**Boys (N=61259)**
Age*, median (quartiles)	5 (1-9)	5 (1-9)
LTI = Epilepsy, n (%)	11541 (22,2)	13470 (22,0)
CMUC, n (%)	15719 (30,2)	19780 (32,3)
Hospitalization for epileptic seizure†, n (%)	14449 (27,7)	17497 (28,6)
Initiation of an antiepileptic treatment†, n (%)	42493 (81,6)	50064 (81,7)
Annual density of prescription of AED‡, median (quartiles)	11,9 (8,8 - 12,2)	11,7 (8,7-12,2)
Number of ATC classes experimented by child†, n (%)		
1 class	27126 (52,1)	31700 (51,7)
2 classes	14508 (27,8)	17640 (28,8)
>=3 classes	10469 (20,1)	11919 (19,5)
Taking AED treatment**, n (%)		
Sodium valproate	27508 (52,8)	35873 (58,6)
Diazepam	16227 (31,1)	20529 (33,5)
Lamotrigine	8813 (16,9)	7493 (12,2)
Levetiracetam	8406 (16,1)	9043 (14,8)
Clobazam	7988 (15,3)	9229 (15,1)
Clonazepam	6824 (13,1)	8163 (13,3)
Carbamazepine	4161 (8,0)	5615 (9,2)
Topiramate	3416 (6,6)	3605 (5,9)
Ethosuximide	2711 (5,2)	2471 (4,0)
Oxcarbazepine	2603 (5,0)	3242 (5,3)
Phenytoine	209 (0,4)	261 (0,4)
Majority type of AED prescriptions†, n (%)		
>50% of prescriptions in monotherapy without VPA	25539 (49,0)	26525 (43,3)
>50% of prescriptions in monotherapy with VPA	19019 (36,5)	25743 (42,0)
>50% of prescriptions in polytherapy without VPA	2030 (3,9)	2219 (3,6)
>50% of prescriptions in polytherapy with VPA	2877 (5,5)	3611 (5,9)
No majority type of AED prescriptions	2638 (5,1)	3161 (5,2)

** Parameter calculated at the beginning of the study period, i.e. the first of January 2010.*

† *Parameter calculated over the study period (From 2010 until 2016).*

‡ *Parameter calculated over the period of prescription (from the first prescription until the last prescription identified over the study period before the age of 14.*

*** At least one supply of the AED before the age de 14 and over the study period.*

LTI denotes long-term illness status which gives entitlement to full health care reimbursement, CMUC Complementary Universal Health Insurance status, which provides information on the patients' socio-economic level, AED antiepileptic drug, ATC Anatomical Therapeutic Chemical.

Table 2: Proportion of VPA among AED treatment initiations, by prescriber category.

Sodium valproate			2010	2011	2012	2013	2014	2015	2016*
Girls 0-14 years	Hospital practitioner**	N	4243	4330	4325	4320	4195	4081	2255
		n	1807	1740	1703	1721	1552	1343	495
		%	42.59	40.18	39.38	39.84	37.00	32.91	21.95
	General practitioner	N	1901	1684	1378	1243	1223	1184	645
		n	438	406	426	372	360	281	130
		%	23.04	24.11	30.91	29.93	29.44	23.73	20.16
	Pediatrician	N	288	275	275	237	246	233	130
		n	138	122	130	116	107	110	42
		%	47.92	44.36	47.27	48.95	43.50	47.21	32.31
	Neurologist	N	428	348	338	338	339	336	172
		N	177	145	131	132	116	80	29
		%	41.36	41.67	38.76	39.05	34.22	23.81	16.86
Boys 0-14 years	Hospital practitioner**	N	5250	5357	5199	5054	5071	4913	2853
		n	2348	2323	2199	2145	2119	1946	1082
		%	44.72	43.36	42.30	42.44	41.79	39.61	37.92
	General practitioner	N	2083	1979	1590	1437	1401	1273	653
		n	523	546	602	469	421	351	153
		%	25.11	27.59	37.86	32.64	30.05	27.57	23.43
	Pediatrician	N	299	295	327	307	319	289	149
		n	142	129	130	152	164	131	66
		%	47.49	43.73	39.76	49.51	51.41	45.33	44.30
	Neurologist	N	401	357	311	357	310	308	167
		n	177	171	159	162	146	126	58
		%	44.14	47.90	51.13	45.38	47.10	40.91	34.73

N = number of prescriptions initiated by the prescriber category
n = number of prescriptions of VPA among the previous N
**up to 31/07/2016*
***physician working in a hospital, considered as a specialist*

Highlights:

- Since 2010, initiations of VPA have decreased among girls aged 0 to 14 years.
- Initiations of LTG and LEV increased among girls over the study period.
- In 2016, GPs were still initiating VPA among girls aged 11-14 years.
- GPs remain the primary healthcare professionals for epileptic patients.
- ~~VPA is still the drug of choice for first-line treatment.~~

Abstract

Purpose

After a huge campaign of information on the teratogenic risk of sodium valproate (VPA) having taken place in France we aimed to evaluate the trend of its prescriptions in young epileptic girls.

Method

Using the French National Health Insurance Database we searched for patients aged 0 to 14 years being supplied an antiepileptic drug (AED) between 2010 and 2016.

Results

113,362 children received at least one AED, 61,259 boys and 52,103 girls. Compared to 2010-2014 years, VPA was less prescribed in 2016 as first AED (29% vs 37.3% respectively). The difference between the two periods was greater for girls (-41%) than for boys (-12%).

Conclusion

The changing trend of VPA as first AED prescribed, particularly in girls, reflects published evidence in terms of safety.

Trends in sodium valproate prescriptions among children aged 0 to 14 years between 2010 and 2016: A study based on the French National Health Insurance Database.

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- Initiations of LTG and LEV increased among girls over the study period.
- In 2016, GPs were still initiating VPA among girls aged 11-14 years.
- GPs remain the primary healthcare professionals for epileptic patients.

Abbreviations:

AED	Antiepileptic drugs
ANSM	Agence Nationale de Sécurité des Médicaments des produits de santé (French agency for the safety of medicines and health products)
ATC	Anatomical Therapeutic Chemical
CCAM	Classification Commune des Actes Médicaux
CIP	Code identification produit (national registration code)
CMUc	Couverture médicale universelle complémentaire (Complementary Universal Health Insurance)
DCIR	Données de Consommation Inter-Régimes (Health reimbursement database)
DP	Diagnostic principal (main diagnose)
DR	Diagnostic relié (related diagnose)
DAS	Diagnostic associé significatif (significant related diagnose)
EEG	Electroencephalogram
EMA	European Medicines Agency
GP	General practitioner
ICD	International Classification of Diseases
LEV	Levetiracetam
LTI	Long-Term Illness
LTG	Lamotrigine
PMSI	Programme de Médicalisation du système d'information (French hospital discharge database)
PY	Person-Year
SNIIRAM	Système National d'Information Inter-Régimes de l'Assurance Maladie (French National Health Insurance Database)
VPA	Sodium valproate

1) Introduction

Epilepsy is one of the commonest serious chronic neurological disorders. Worldwide there are at least 65 million people living with epilepsy. The incidence of epilepsy in the infantile period is high, with an estimation of about 70 per 100,000 inhabitants in European countries. [1]

The management of epilepsy among children is different from that among adults because of a broader spectrum of syndromes in children and because evidence on the effectiveness of antiepileptic drugs (AEDs) is not always established. [2–4] A therapeutic choice must still be made even if a precise diagnosis is not straightforward at the onset of epilepsy.

In the 2000s, new AEDs arrived on the drug market and changed practices in the treatment of epilepsy for both children and adults. [5,6] The changes could also be related to an awareness of the risks associated with in utero exposure to earlier antiepileptic drugs, such as sodium valproate (VPA), which has been integrated into clinicians' practices, especially neurologists, as demonstrated in Europe and across the Atlantic. [7–9] In 2014, as recommended by the European Medicines Agency (EMA), the French Agency for the safety of medicines and health products (ANSM) initiated a communication strategy with a "Dear Doctor" letter [10] to remind healthcare professionals of the teratogenic effects of VPA (major congenital malformations [11], neuro-developmental delays [12], autism spectrum disorders [13,14]). A few months later, in May 2015, French clinicians were also informed that the conditions for prescription and issue of VPA and its derivatives would be reinforced. [15] Since the 1st of January 2016, VPA and its derivatives should, whenever it is possible, not be prescribed to women of childbearing age, except in case of intolerance or ineffectiveness of alternatives. Nonetheless, the unchallenged efficacy of VPA, with its broad spectrum of activity, makes it a drug of choice for the first-line treatment of epilepsy.[16] More recently in Europe, likewise,

VPA has been contraindicated for women of reproductive potential, except in case of intolerance or ineffectiveness of alternatives.

We aimed to evaluate trends in AED prescriptions, especially in the period 2015-2016, to tailor a communication strategy, focusing on young epileptic girls, for whom VPA should not be chosen as the first-line treatment.

1) Methods

We conducted a nationwide study using the French National Health Insurance Database (SNIIRAM), over 7 years (2010-2016), to describe the trends in VPA prescription among epileptic girls 0 to 14 years of age, particularly as first-line treatment, and we compared this with prescribing trends for boys aged 0 to 14 years.

Source

SNIIRAM anonymously and comprehensively links a health reimbursement database (DCIR) to the French hospital discharge database (PMSI). The DCIR contains i) demographic data such as date of birth, gender and information on complementary insurance systems or the presence of CMUc (Couverture médicale universelle complémentaire) (Complementary Universal Health Insurance), an insurance cover for low-income status individuals ii) medication, recorded as dispensed packs, including a single national registration code (CIP), and Anatomical Therapeutic Chemical (ATC) code is also provided with the date of prescription, the profession of the prescriber and date of issue iii) the presence of long-term illness (LTI) status and date of first registration of chronic illness status, which gives registered patients full coverage for all medical expenses related to the illness. PMSI covers all overnight or day hospitalizations in the public and private sectors, and includes short-term stays in medical, surgical or obstetric facilities. It collects information on the patients and their diagnoses (primary diagnoses (DP—diagnostic principal /DR—diagnostic relié) (main and related diagnoses)) and comorbidities or complications (DAS—Diagnostic associé significatif) (significant related diagnoses) using ICD10 codes (International Classification of Diseases, 10th revision), surgical/interventional procedures (CCAM–Classification Commune des Actes Médicaux) and prescription of particularly expensive drugs.

The SNIIRAM database was developed to ensure the reimbursement of individual medical claims but was not intended to serve medical research. It does not comprise any clinical information concerning results related to consultations, prescriptions or examinations. Using it to follow individual patients over time and across different data sets can therefore be challenging.

It has previously been used to describe prescription trends with respect to recommendations [17] in the context of epilepsy management [18] and VPA exposure [19].

Patient selection

All patients aged 0 to 14 years with at least one issue of antiepileptic drug (AED) recorded between 2010 and 2016 were selected. An AED was defined as a drug licensed for the treatment of epilepsy in France, i.e. drugs listed under the ATC code N03A, plus two benzodiazepines, diazepam (N05BA01) and clobazam (N05BA09). As diazepam is mainly authorized for febrile convulsions, patients who were prescribed diazepam only were excluded. Patients, who were prescribed sodium divalproex (N03AG01) or valpromide (N03AG02) were also excluded because these medications are mostly indicated in psychiatric setting.

Data collection

For descriptive purposes different patient characteristics were collected: date of birth to determine the age at the beginning of the study (January 1st, 2010), gender, LTI status, CMUc status, which provides information on patient socio-economic level. Prescription characteristics were obviously studied: date of prescription, date of issue, drug issued, number of boxes and also information on the prescriber, as working in a healthcare facility or in the community.

Statistical analysis

For each patient matching the selection criteria and for each prescription we determined whether it was a prevalent or an incident use (first delivery after birth or after one year without AED issue). A one-year history was necessary to obtain this information and this is the reason why we retrospectively collected data up to 2009. We also determined which AEDs were prescribed (grouping them by ATC7 Code). The number of different ATC7 codes prescribed defined the polytherapy criterion.

For each year, we first calculated the percentage of VPA and that of each ATC7 code other than VPA among incident uses, and plotted these proportions by gender and age category. We use the following age categories: 0-2 years, 3-6 years, 7-10 years and 11-14 years. For purposes of comparison, we calculated the relative reduction in prescriptions between the percentage of VPA prescribed in 2010-2014 and the one in 2016. We intentionally excluded the year 2015, during which time the EMA and ANSM promoted a huge campaign to avoid the use of VPA among women of childbearing age. The impact of the 2015 risk minimization measure was likely to be more obvious in 2016, the year we chose for comparison.

We then calculated the incidence rate of VPA prescription among prevalent uses of any other AEDs and plotted them by gender and age category: the number of VPA initiations was divided by the number of person-years (PY) with a prevalent use of another AED. The types of AED before VPA initiation were described.

Finally we calculated the incidence rate for VPA discontinuations among prevalent users of VPA and the proportion for each ATC7 code among AED prescriptions after VPA discontinuation. VPA discontinuation was defined by the last VPA delivery date followed by at least one year without VPA issue, assuming one year of follow-up was available.

Statistical analyses were performed using SAS 9.4 (SAS INSTITUTE, North Carolina, USA) via SAS Enterprise Guide®.

Regulatory approval

The study was granted regulatory approval as part of a larger program on VPA exposure (CNIL 03/11/2016). The study was conducted with direct access to the SNIIRAM database under ANSM agreement.

2) Results

General characteristics of the study population

In the SNIIRAM database, 113,362 children fulfilled the selection criteria, 61,259 boys and 52,103 girls. Almost all patient characteristics were similar between boys and girls (Table 1). The number of incident uses over the study period (seven years) was 93,557: 42,493 among girls and 50,064 among boys. The median age at the beginning of the study was five years.

The most frequently prescribed antiepileptic drugs were, in decreasing order: sodium valproate, largely predominant, followed by diazepam, lamotrigine (LTG), levetiracetam (LEV), clobazam and clonazepam. Most of the drugs were prescribed in monotherapy.

Prescribing trends for sodium valproate

Figure 1 shows the trends in VPA initiations over the study period by gender and age category. Focusing on children aged 0-10 years and incident uses only in 2010, the proportion of VPA prescriptions ranged between 40 and 50%, without a clear gap between boys (nearly 30%) and girls (20%). Globally, the proportion remained quite stable until 2014 and then decreased. In 2016, the proportion of VPA still accounted for 11% of AED initiations among girls aged 11-14 years.

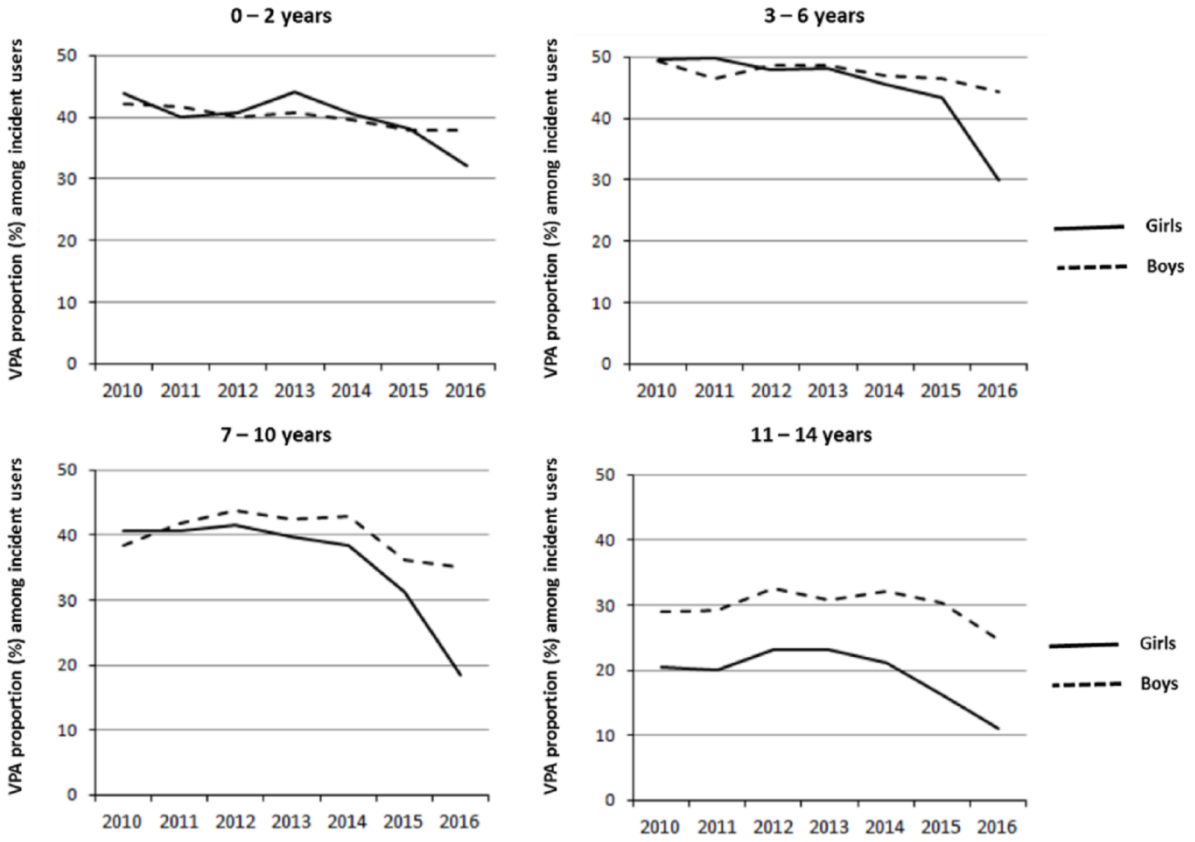


Figure 1. Trends in sodium valproate initiations over the study period by gender and age category. *(2-column fitting image)*

Between 2010 and 2016, the proportions of prescriptions for LEV, LTG, ethosuximide, gabapentin in incident use increased among girls aged 0-14 years (Figure 2).

Table 2 reports the proportion of VPA among AED initiations according to prescriber category. In 2010, initiation of VPA among girls by specialists (including hospital practitioner and neurologist or pediatrician working in community) was relatively frequent (over 40%). This frequency was lower in 2016 for neurologists (-24.5% between 2010 and 2016), hospital practitioners (-20.6%) and pediatricians (-15.6%). In contrast, the frequency of VPA use among AED initiations by General Practitioners (GPs) was relatively stable over the period, at around 20-25%.

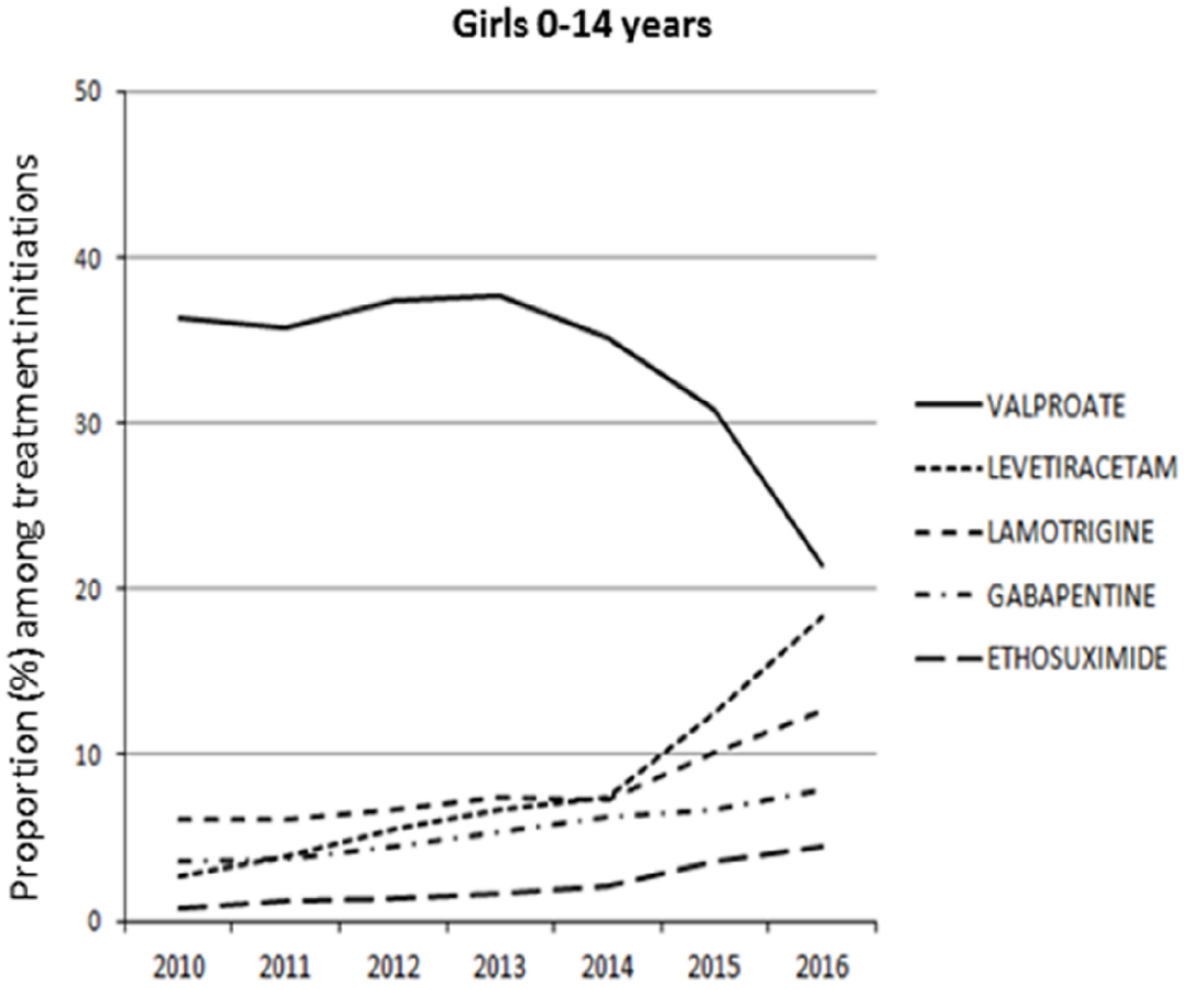


Figure 2. Trends in antiepileptic treatment initiations over the study period among girls aged 0-14 years. *(1-column fitting image)*

Figure 3 shows trends in initiating VPA (add-on or switch) among prevalent users of any AED other than VPA over the study period by gender and age category. The number of PY treated with an AED other than VPA was around 5000 per year over the study period. In this population, the incidence rate for VPA prescription decreased from 18.3 in 2010 to 9.7 per 100 PY in 2016 for girls (47% relative reduction) versus 20.3 to 16.1 per 1000 PY for boys (relative reduction of 21%). These relative reductions were homogeneous across the different age groups.

It can be noted that the incidence rate for VPA prescription among teenage girls (11-14 years of age) and young girls (7-10 years of age) was relatively low over the study period (less than 10 for 100 PY). The most frequently prescribed AEDs just before VPA initiation were benzodiazepines, lamotrigine and vigabatrine, mostly in monotherapy (91% in 2010; 89% in 2015).

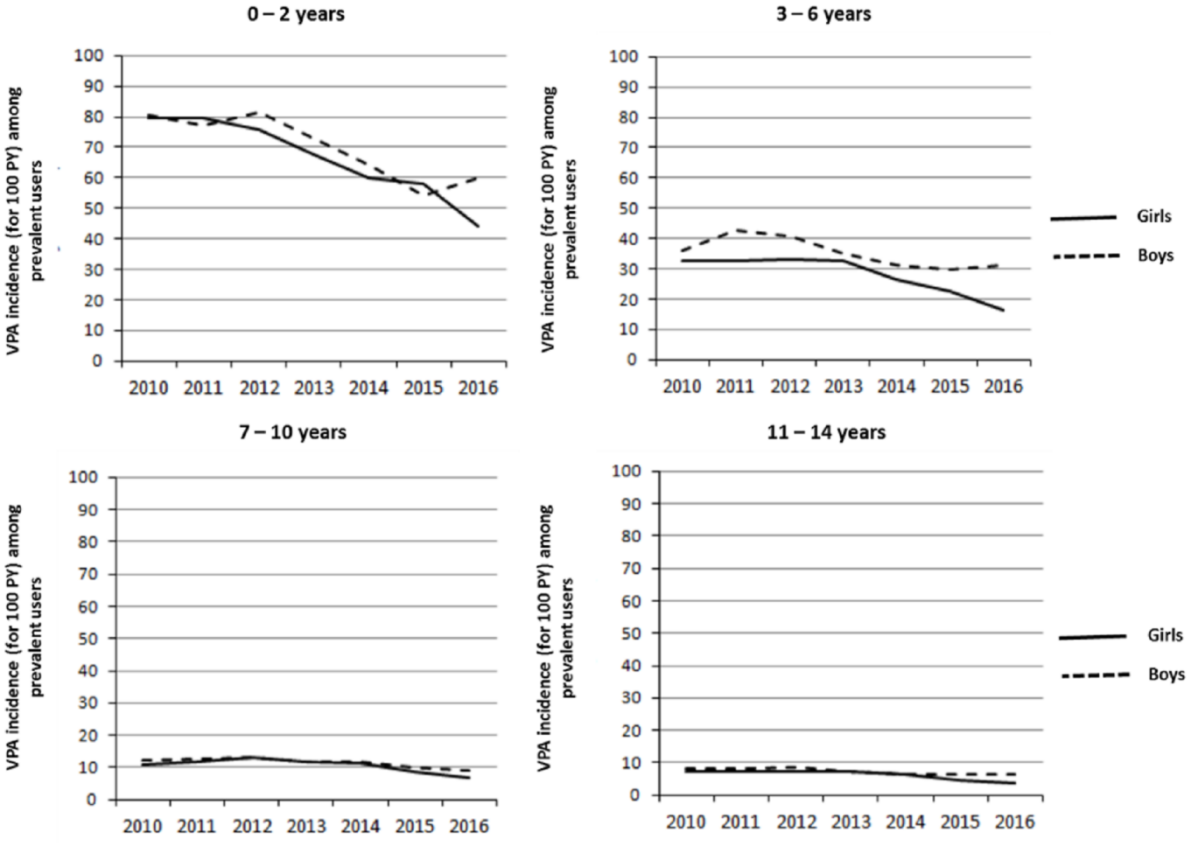


Figure 3. Trends in sodium valproate initiations (add-on or switch) among children already treated with another antiepileptic drug over the study period, by gender and age category. *(2-column fitting image)*

Discontinuation of VPA was defined as an issue of VPA that was not followed later in the year by another issue of VPA, assuming one year of follow-up was available. Discontinuation of VPA was quite high (around 35 per 100 child-years) but quite stable over the study period and similar in girls and in boys. It was higher among young children (0-6 years old) than among older children (7-14 years old) (40 to 60 per 100 PY versus 30 per 100 PY).

In around 70% of cases, VPA discontinuation was not followed by another AED. Before withdrawal of sodium valproate treatment, the antiepileptic treatment duration was for the majority 1 year or more (60%), while in 18% of cases it was less than 1 month (only 1 issue). It was different among children aged 0-2 years, for whom only 1 month of antiepileptic treatment before VPA withdrawal was observed in 30% of cases.

The remaining 30% “switched” from VPA to another AED, mostly in monotherapy. Lamotrigine and levetiracetam were the most frequently prescribed AEDs.

Discussion

Our study evaluating the trends in sodium valproate (VPA) prescription among children highlighted a number of points.

Firstly, the proportion of VPA prescriptions among incident uses of antiepileptic drugs decreased in both genders over the study period, but more so among girls, especially in teenage girls. Over the 1993 to 2006 period, the prevalence of VPA per 1000 prescriptions among females (12-18 years old) significantly decreased from 0.94 (95% CI 0.80 to 1.09) to 0.63 (95% CI 0.55 to 0.72). [7]. Over the 2000 to 2010 period, girls were prescribed sodium valproate significantly less often as a first-line AED (74% versus 46%). [20] Our study enables these observations to be updated and it points to a substantial decrease in VPA use among teenage girls, possibly as a result of new information released in the media on its teratogenic effects. [10]

Secondly, the alternatives to VPA, for which frequencies increased during the study period, were mainly levetiracetam, then lamotrigine, followed by ethosuximide and gabapentin. Increases were always more pronounced for girls than for boys. Changes in the choice of the first AED for a new onset of epilepsy are similar to those observed in previous years in other European countries. [7,9,20] During the 2000s, it was established that the use of first-generation AEDs (VPA, carbamazepine, phenytoin, phenobarbital) decreased over time, at least in developed countries, concomitantly with the arrival of new AEDs on the market. [5,9,21,22] More recently, a trend towards more LEV and LTG prescriptions could also be explained by prescribers' knowledge of the significantly lower rates of major congenital malformations for these drugs. [11]

Thirdly, the proportion of VPA initiations among girls already under treatment greatly decreased for specialists but remained stable over the study period for GPs. The proportions of AED prescriptions by three different prescriber categories (GPs, specialists, psychiatrists) were studied by Hollingworth & al. in Australia over a 5-year period (2002-2007). They observed an increase in prescribing of new AEDs, such as levetiracetam, topiramate and lamotrigine, by GPs. Also, the proportion of prescriptions by GPs was the highest for phenytoin, followed by sodium valproate. [23] Prescriber data in this study indicated a shift from specialist to GP prescribing. Neurologists commonly initiate AED prescription for epilepsy and the subsequent prescribing is usually taken on by GPs. This pattern should be applied in France according to the latest recommendations. Nevertheless, VPA accounted for 20% of AEDs initiated by a GP. In the clinical context of epilepsy, primary care should lead to an initiation of antiepileptic treatment to limit possible seizures and should not have to be delayed until the final therapeutic choice made by a specialist. Continuing prescription of VPA as first-line treatment by GPs could reflect difficulties in healthcare trajectories for the French epileptic population, with difficult access to specialized care (EEG, neurologist, tertiary care hospitals), compelling GPs to ensure the care of first seizures with VPA, on the grounds that this AED has a broad spectrum of activity.

Finally, discontinuation of VPA was stable over the study period, among girls but also among boys, and did not seem to be influenced by the recommendations. In 70% of cases, the withdrawal of VPA was not followed by another AED, and this was all the more true among children aged 0-2 years. The exact reasons why treatments were discontinued is not known, but some situations can justify it. For instance, treatment with VPA can be discontinued after a diagnosis of recovery. VPA is the drug of choice for many epileptic syndromes, and widely prescribed by GPs. After specialist consultation or access to electroencephalogram (EEG), a

diagnosis other than epilepsy can be made. An antiepileptic treatment can also be prescribed on a temporary basis, for example in case of accidental seizure after meningitis, head trauma, or febrile seizures. In these cases, the treatment duration is short (a few months) and pursuit of antiepileptic treatment is not expected. Among older children, discontinuation of the antiepileptic treatment can occur in certain types of syndrome (childhood absence epilepsy, benign rolandic epilepsy) after a seizure-free period, or to limit the neurocognitive impact of AEDs. Prolonged discontinuations do not systematically lead to seizure recurrence and are possible for some patients. [30, 31]

Compared to previous studies, our investigation, by using a large population database over a recent period of time, is the first one that evaluates latest trends in prescribing valproate focusing on children.

A first limitation is the definition of incident use, which could include a re-instatement of treatment, as it was based on a one-year AED-free period only. However, recommendations on VPA use encompass AED initiation as well as resumption of treatment. A second limitation is the fact that the SNIIRAM database does not enable the pathological context of prescriptions to be identified because no clinical data is available except for the hospital discharge diagnoses.. Nevertheless, we believe that AEDs are primarily prescribed in children for anticonvulsant purposes and, more importantly, our objective was to observe a decrease in valproate prescribing trends regardless of indication. Finally, patients in long-term facilities were not included in this study because AED issues for these patients were not available in the database. These patients often have pharmaco-resistant epilepsy, or at least epilepsy that is hard to stabilize with different AED prescription strategies. [23, 24]

Conclusion

This large-scale study describes changes in paediatric prescription patterns following the implementation of a national information campaign on the appropriate use of VPA.

The observed trend was as expected, with a decrease in VPA initiations, especially after 2015, among children whether or not already treated with an AED. This decrease was observed in both genders, more pronounced for girls, and sharper in 2016. The proportion of VPA prescriptions among the different AED prescriptions decreased between 2010 and 2016 in favor of LTG and LEV, often used as monotherapy. Whatever the nature of the prescription (initiation or not), they came mainly from hospital prescribers (specialists) and from neurologists or pediatricians.

All prescribers reduced VPA prescriptions between 2010 and 2016, especially the neurologists. VPA initiation remained stable among GPs. In 2016, the Prescription and Drug Supply Conditions changed for VPA in France: it is now mandatory for it to be initiated by a specialist. Furthermore, the European Medicines Agency recently changed the recommendations for VPA use: it should not be prescribed to women of childbearing potential except if there is no other treatment option, and provided the woman is on adequate contraception. Further evaluations in 2016, 2017 and 2018 could be valuable.

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Table 1: Characteristics of the study population.

	Girls (N=52103)	**Boys (N=61259)**
Age*, median (quartiles)	5 (1-9)	5 (1-9)
LTI = Epilepsy, n (%)	11541 (22,2)	13470 (22,0)
CMUC, n (%)	15719 (30,2)	19780 (32,3)
Hospitalization for epileptic seizure†, n (%)	14449 (27,7)	17497 (28,6)
Initiation of an antiepileptic treatment†, n (%)	42493 (81,6)	50064 (81,7)
Annual density of prescription of AED‡, median (quartiles)	11,9 (8,8 - 12,2)	11,7 (8,7-12,2)
Number of ATC classes experimented by child†, n (%)		
1 class	27126 (52,1)	31700 (51,7)
2 classes	14508 (27,8)	17640 (28,8)
>=3 classes	10469 (20,1)	11919 (19,5)
Taking AED treatment**, n (%)		
Sodium valproate	27508 (52,8)	35873 (58,6)
Diazepam	16227 (31,1)	20529 (33,5)
Lamotrigine	8813 (16,9)	7493 (12,2)
Levetiracetam	8406 (16,1)	9043 (14,8)
Clobazam	7988 (15,3)	9229 (15,1)
Clonazepam	6824 (13,1)	8163 (13,3)
Carbamazepine	4161 (8,0)	5615 (9,2)
Topiramate	3416 (6,6)	3605 (5,9)
Ethosuximide	2711 (5,2)	2471 (4,0)
Oxcarbazepine	2603 (5,0)	3242 (5,3)
Phenytoine	209 (0,4)	261 (0,4)
Majority type of AED prescriptions†, n (%)		
>50% of prescriptions in monotherapy without VPA	25539 (49,0)	26525 (43,3)
>50% of prescriptions in monotherapy with VPA	19019 (36,5)	25743 (42,0)
>50% of prescriptions in polytherapy without VPA	2030 (3,9)	2219 (3,6)
>50% of prescriptions in polytherapy with VPA	2877 (5,5)	3611 (5,9)
No majority type of AED prescriptions	2638 (5,1)	3161 (5,2)

** Parameter calculated at the beginning of the study period, i.e. the first of January 2010.*

† *Parameter calculated over the study period (From 2010 until 2016).*

‡ *Parameter calculated over the period of prescription (from the first prescription until the last prescription identified over the study period before the age of 14.*

*** At least one supply of the AED before the age de 14 and over the study period.*

LTI denotes long-term illness status which gives entitlement to full health care reimbursement, CMUC Complementary Universal Health Insurance status, which provides information on the patients' socio-economic level, AED antiepileptic drug, ATC Anatomical Therapeutic Chemical.

Table 2: Proportion of VPA among AED treatment initiations, by prescriber category.

Sodium valproate			2010	2011	2012	2013	2014	2015	2016*
Girls 0-14 years	Hospital practitioner**	N	4243	4330	4325	4320	4195	4081	2255
		n	1807	1740	1703	1721	1552	1343	495
		%	42.59	40.18	39.38	39.84	37.00	32.91	21.95
	General practitioner	N	1901	1684	1378	1243	1223	1184	645
		n	438	406	426	372	360	281	130
		%	23.04	24.11	30.91	29.93	29.44	23.73	20.16
	Pediatrician	N	288	275	275	237	246	233	130
		n	138	122	130	116	107	110	42
		%	47.92	44.36	47.27	48.95	43.50	47.21	32.31
	Neurologist	N	428	348	338	338	339	336	172
		N	177	145	131	132	116	80	29
		%	41.36	41.67	38.76	39.05	34.22	23.81	16.86
Boys 0-14 years	Hospital practitioner**	N	5250	5357	5199	5054	5071	4913	2853
		n	2348	2323	2199	2145	2119	1946	1082
		%	44.72	43.36	42.30	42.44	41.79	39.61	37.92
	General practitioner	N	2083	1979	1590	1437	1401	1273	653
		n	523	546	602	469	421	351	153
		%	25.11	27.59	37.86	32.64	30.05	27.57	23.43
	Pediatrician	N	299	295	327	307	319	289	149
		n	142	129	130	152	164	131	66
		%	47.49	43.73	39.76	49.51	51.41	45.33	44.30
	Neurologist	N	401	357	311	357	310	308	167
		n	177	171	159	162	146	126	58
		%	44.14	47.90	51.13	45.38	47.10	40.91	34.73

N = number of prescriptions initiated by the prescriber category
n = number of prescriptions of VPA among the previous N
**up to 31/07/2016*
***physician working in a hospital, considered as a specialist*

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Supporting files

Not applicable. No supporting files.