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Changes in the use of antiseizure medications in children and adolescents in Norway, 2009–2018

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ABSTRACT

Background: The use of antiseizure medications (ASMs) in the pediatric population is poorly studied. The purpose of this study was to investigate changes in the use of ASMs in children and adolescents compared to adults, and to elucidate safety considerations of certain drugs.
Method: In this population-based pharmacoepidemiological study we used the Norwegian Prescription Database (NorPD), 2009–2018. The use of ASMs is presented as 1-year prevalence per 1000: number of ASM users in a year * 1000 / number of inhabitants that year. Variables included predetermined 5-year age groups, gender, ASMs, diagnosis-specific reimbursement codes, user, and population numbers. Selected ASMs used for specific indications or subgroups included ethosuximide, sulthiame, rufinamide, stiripentol, and clobazam. Gender differences in the use of valproate was examined due to safety considerations in girls/women.
Results: The total number of ASM users (all indications) for the age groups 0–19 and 20–59 years was 5807 and 47,481 respectively in 2009, and 5906 and 61,447 respectively in 2018. The 1-year prevalence for children/adolescents (0–19 years) using ASMs in epilepsy remained stable from 2008 to 2018, 4.3–4.2/1000 inhabitants, as compared to 8.2–7.6/1000 in adults (20–59 years). Valproate, lamotrigine, and levetiracetam were the three most used ASMs in epilepsy in children/adolescents, similar to adults. The selected ASMs were mainly used in children/ adolescents, accounting for 0.74/1000 in 2018 versus 0.17/1000 in adults. A significant increase was seen for sulthiame (8-fold), ethosuximide (4-fold), clobazam (3-fold), and stiripentol (2-fold). The use of ASMs in non-epilepsy indications was limited and stable (17% in 2018); mainly lamotrigine in psychiatry in adolescents (15–19 years). This finding was in contrast to extensive non-epilepsy use in adults (71% in 2018).
Conclusion: Changes in the use of ASMs in children/adolescents differ as compared to adults, most notably extensive and increasing use of selected ASMs and limited non-epilepsy. This is an important part of pharmacovigilance and patient safety evaluations.

1. Introduction

Epilepsy is one of the most common neurological disorders and affects 0.5–1% of the pediatric population, with a prevalence in children and adolescents of 3.2–4.1 per 1000 inhabitants (Syvertsen et al., 2015; Aaberg et al., 2017). Childhood epilepsies are heterogenous and differ in severity, and these patients constitute a vulnerable group, where the use of antiseizure medications (ASMs) is scarcely described. A number of different ASMs are now available in Norway, and they have various indications, pharmacological properties and challenges such as adverse effects and drug interactions (Johannessen Landmark et al., 2016).

Changes in the use of drugs may be followed closely at the population

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level and in subgroups of patients, as part of pharmacovigilance or drug surveillance. We have used the Norwegian Prescription Database (NorPD) in previous studies with focus on changes in the use of ASMs in epilepsy and other indications in adults and elderly (Johannessen Landmark et al., 2009, 2011; Karouni et al., 2010; Baftiu et al., 2016, 2018). In previous patient-oriented studies of subgroups of patients with epilepsy, we have observed changes in the use of specific drugs in children and sex differences in young adults regarding the choice of ASMs (Johannessen Landmark et al., 2019; Heger et al., 2020). In the present study we used a pharmacoepidemiological approach to further clarify trends and changes in the treatment with ASMs across the total population in Norway. By investigating prescription patterns of ASMs in large patient populations, we are able to identify certain trends or safety issues related to specific ASMs which may then be studied in more detail in subgroups of patients, e.g., young children or adolescents. The purpose of this study was to investigate changes in the use of ASMs in children and adolescents over the past decade as compared to adults in Norway, and to elucidate safety considerations of certain drugs.

2. Methods

This study was a population-based pharmacoepidemiological study using data from The Norwegian Prescription Database (NorPD), which is a validated population-based data source (Wettermark et al., 2013). A research file was provided by NorPD and included all prescriptions of ASMs with reimbursement, reflecting chronic use. All data were pseudonymised before we received the data file, with no patient identification. Each patient is given a running number in the data file (pseudonymous) from a third party, Statistics Norway, as described in detail by Furu (2008). Drugs used to treat epilepsy, ASMs, dispensed from all pharmacies in Norway during the period 2009–2018 were included. Variables included sex, pre-determined 5-year age groups, encrypted person identifiers instead of identity, prescription category (public refund or no refund) and specific codes for reimbursement and indication (ICD-10/ ICPC-2).

2.1. Specifications of the included drugs

Classification of drugs was according to the Anatomical Therapeutic Chemical (ATC) classification codes: All ASMs (N03A) approved and marketed in Norway were regarded as drugs used to treat epilepsy and thus included in the search (Table 1). In addition, clobazam (N05B09) and sulthiame were included. These two drugs are not marketed in Norway but are available and are commonly used in the treatment of epilepsy. Retigabine was withdrawn from the Norwegian marked as late as 2018 and was therefore included. The selected ASMs were studied in detail because they are used for specific indications, in rare epilepsy syndromes or in subgroups such as very young children, and included ethosuximide, sulthiame, rufinamide, stiripentol and clobazam (Table 1). In addition, sex differences for valproate were studied, due to the recent restrictions in use in girls and women of child-bearing age (Tomson et al., 2015, 2019). Finally, the use of the most recently approved ASMs (after 2008) was studied and included brivaracetam, lacosamide, eslicarbazepine and perampanel.

Table 1
Definitions of variables and calculations included.

Variable	Details
Age groups	• Children/adolescents: 0–19 years, and 5-year groups: 0–4, 5–9, 10–14, 15–19 years, where 15–19 was regarded as adolescents • Adults: 20–59 years. Older age groups for comparison were excluded
Patient-related variables	• Number of users • Population data • Prescription reimbursement (§2, 3a and 3b) • Specific reimbursement codes (see below)
All included drugs (ATC-code)	• All antiseizure medications (N03A): brivaracetam, carbamazepine, clonazepam, eslicarbazepine, ethosuximide, felbamate, gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, perampanel, phenobarbital, phenytoin, pregabalin, retigabine, rufinamide, stiripentol, sulthiame, topiramate, valproate, vigabatrin, zonisamide
ASMs studied in detail:Special and selected ASMs, defined as used in specific indications or subgroups of patientsSex differences and safety considerationsThe most recently approved ASMs (approved in Norway after 2008)	• Clobazam (N05BA09) • Clobazam: not classified as an ASM (see above), not marketed in Norway • Ethosuximide: used only in absence seizures • Sulthiame: used mainly in children with childhood epilepsies, not marketed in Norway • Rufinamide and stiripentol: Used only in Lennox Gastaut and Dravet syndrome, respectively • Valproate: restrictions in use in girls and women of child-bearing age, sex differences • Brivaracetam, lacosamide, eslicarbazepine, perampanel
Reimbursement codesICPC-2 (primary healthcare service) diagnoses are coded according to the International Classification of Primary Care second version (ICPC-2).ICD -10 (specialist healthcare service)Diagnoses in the NorPD are coded according to the International Classification of Diseases, 10th revision (ICD-10).	• N88 (epilepsy) • N89 (migraine) • -71 (chronic pain) • -73, -74, P73, P74, P76 (psychiatry) • G40 (epilepsy) • G43 (migraine) • -71 (chronic pain) • F2, F3, F4, F30, F31, F32, F33, F41 (psychiatry)
Calculations1-year prevalence per 1000:1-year prevalence per 1000 in a sub-group: Percentage of use in various age groups:	Number of users in a year *1000 / number of inhabitants that year. A *user* is defined as a person who has had at least one prescription dispensed in a pharmacy during the period. Number of users in a year *1000 / number of inhabitants that year stratified on sub-group % of number of users for each drug in 2018 in various age groups. Note that patients could use more than one ASM

Table 2
Use of ASMs in various indications among the age groups.

1-year prevalence per 1000 and use of ASMs	Children					Adults	Total population
	0–4 years	5–9 years	10–14 years	15–19 years	Total, 0–19 years	Total, 20–59, years	0–90+ years
Number of inhabitants[a]							
2009	271,605	297,456	314,302	320,634	1,203,996	2,592,541	4,829,800
2018	266,636	319,749	319,364	319,665	1,225,413	2,845,321	5,311,797
All indications, 1-year prevalence per 1000							
2009	1.9	4.0	5.8	7.2	4.8	18.3	16.4
2018	2.1	4.1	5.4	7.2	4.8	21.6	20.9
Epilepsy, 1-year prevalence per 1000							
2009	1.8	3.9	5.4	5.5	4.3	8.2	7.8
2018	2.0	4.0	5.0	5.3	4.2	7.6	7.8
Non-epilepsy indications, total[b], 1-year prevalence per 1000							
2009	0.03	0.16	0.53	1.9	0.68	12.0	10.1
2018	0.12	0.28	0.64	2.2	0.83	15.0	14.2
Specific non-epilepsy indications, total 1-year prevalence per 1000							
Psychiatry							
2009	0.03	0.12	0.41	1.56	0.56	6.0	4.1
2018	0.04	0.18	0.38	1.51	0.55	6.3	4.8
Neuropathic pain	0						
2009		0.03	0.10	0.27	0.11	5.2	6.0
2018	0.08	0.08	0.2	0.5	0.24	8.2	9.2
Migraine	0						
2009		0.003	0.02	0.03	0.01	0.05	0.03
2018	0.004	0.013	0.04	0.13	0.05	0.32	0.20

[a] Statistics Norway (2021).
[b] The total numbers of non-epilepsy indications also include limited, unspecified use in off-label indications. There are some slight discrepancies in the numbers, due to the fact that some patients may receive the same ASM for different indications or use several ASMs in both epilepsy and in other indications. For small numbers, errors may occur when two decimals are used.

2.2. Patients

Children and adolescents (0–19 years, divided into pre-determined 5-year groups as defined in the NorPD database) were compared to the adult population to investigate changes in the use of the various ASMs and age-specific differences in use. Numbers for the total population (0–90+) are presented in Table 2 to enable comparisons with other studies and other countries' populations.

2.3. Definitions and calculations

The use of ASMs is presented as 1-year prevalence for specific ASMs for each indication, defined as the number of ASM users per 1000 per year in the population. Users are defined as the number of individuals prescribed a dose of an ASM. The most used ASMs in epilepsy were selected with a cut-off value of 1-year prevalence 0.1/1000 users. The non-epilepsy indications were as previously described (psychiatry, neuropathic pain and migraine) (Baftiu et al., 2016). The number of users and user/1000 inhabitants in non-epilepsy indications were calculated by subtracting the users in epilepsy from the total number of users. Further details of definitions and calculations are presented in Table 1. The data are descriptive, and no statistical analyses were performed as the whole population was included. The data were de-identified, as each patient was given a running number in the data file. Statistics Norway provided security for protection of patient information.

3. Results

3.1. 1-Year prevalence and changes in the use of ASMs

The total number of ASM users (all indications) for the age groups 0–19 and 20–59 years was 5807 and 47,481 respectively in 2009, and 5906 and 61,447 respectively in 2018. In 2018 there were 5906 children/adolescents 0–19 years old who had at least one prescription of an ASM regardless of indication, of which 5119 were prescribed an ASM for epilepsy. In children/adolescents, 1-year prevalence of ASM users regardless of indication was unchanged over the decade, in contrast to an increase of 18% in adults (Table 2). The 1-year prevalence of ASM use in epilepsy in children/ adolescents was stable over the decade, mean 4.2 per 1000 children/adolescents, while in adults a slight decrease from 2009 to 2018 (8%) was seen.

3.2. The most common ASMs in epilepsy

In children and adolescents, the most commonly prescribed ASMs in epilepsy during the whole decade were valproate, lamotrigine, and levetiracetam (Fig. 1a). Valproate was extensively used in young patients, whereas in adults, lamotrigine was the most used drug every year throughout the decade (Fig. 1b). Use of carbamazepine was also more extensive in adults during the decade as compared to children/adolescents, whereas levetiracetam was widely used across all age groups. Even though the order differed, the seven most used ASMs were the same in children and adults. Less frequent ASMs included use in the age groups 0–19 and 20–59 years respectively in 2018: gabapentin 0.02 and 0.10, phenobarbital 0.04 and 0.15, phenytoin 0.02 and 0.10, pregabalin 0.01 and 0.40, vigabatrin 0.03 and 0.01, zonisamide 0.07 and 0.14, felbamate 0.007 and 0.009 and retigabine 0 and 0.0004 users per 1000 inhabitants in these age groups.

3.3. Extensive changes in the use of the selected drugs

Selected ASMs in epilepsy were mainly used by children and adolescents and accounted for 0.74/1000 in 2018 (18% of the total use of ASMs in epilepsy): Marked increases were observed for sulthiame (8-fold), ethosuximide (4-fold) and clobazam (3-fold). The use of stiripentol remained relatively stable (Fig. 1c and d). The only drug with a decreased use was rufinamide (by 60%). In contrast, use of the selected

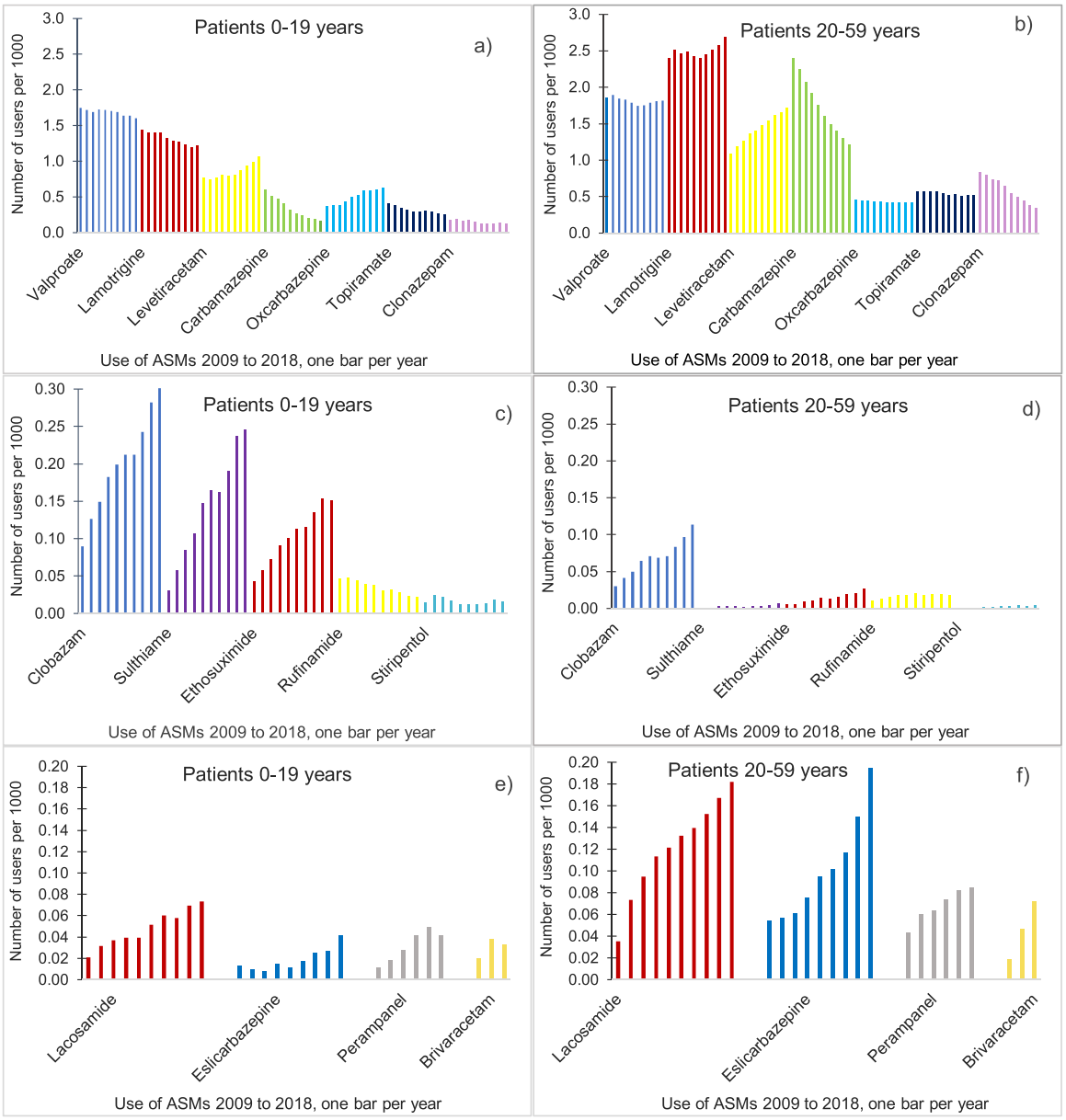

Fig. 1. Changes in the use of top 7 antiseizure medications (ASMs) in children/adolescents (0–19 years) (a) in Norway 2009–2018 and in adults (20–59 years) (b). Each bar represents one year, i.e., every year from 2009 to 2018 is shown in the histograms. Specific ASMs (clobazam, ethosuximide, rufinamide, stiripentol and sulthiame) are shown in children/adolescents (c) and adults (d). The most recently approved ASMs (lacosamide, eslicarbazepine, perampanel and brivaracetam) are shown for children/adolescents (e) and adults (f).

ASMs accounted for as 0.17/1000 in adults in 2018 (2% of the total use of ASMs in epilepsy). The use of clobazam in epilepsy in both children/adolescents and adults increased markedly during the decade (Fig. 1c and d). Epilepsy was the main indication for prescribing clobazam; It doubled and comprised 88% (0.14/1000) of its total use in 2018 as compared to 39% (0.04/1000) in 2009. The total number of users, regardless of indication, increased from 503 to 824, and the increase was most pronounced in children/adolescents (229–384). In 2018 the use of clobazam in children/adolescents was 0.3/1000 while the use of clonazepam was 0.13/1000. In adults, however, the use of clobazam was 0.11/1000 and clonazepam 0.35/1000.

3.4. Limited use of the most recently approved ASMs

The use of the newest ASMs in epilepsy increased during the decade among children/adolescents and adults (Fig. 1e and f). Lacosamide was the most used of these drugs in children/adolescents, whereas the use of perampanel increased most markedly (4-fold). In adults, lacosamide and eslicarbazepine dominated, and the use of lacosamide increased most extensively (5-fold). In 2018, the use of these new drugs accounted for 3% (0.1/1000) of total ASM use in epilepsy in children (0–14 years), and 8% in adolescents (15–19 years) (0.25/1000), while it constituted 7% (0.53/1000) of the total use in adults.

3.5. Use of ASMs in subgroups of patients and sex differences

The use of ASMs among age subgroups in children and adolescents with epilepsy in 2018 is illustrated in Fig. 2a-c. Valproate was widely used in all age groups, but most notably in the 5–9- and 10–14-year groups. The use of lamotrigine increased with age. Levetiracetam was widely used in all age groups and was the most used drug in the youngest age group (0–4 years). Clobazam was mainly used by the older groups,

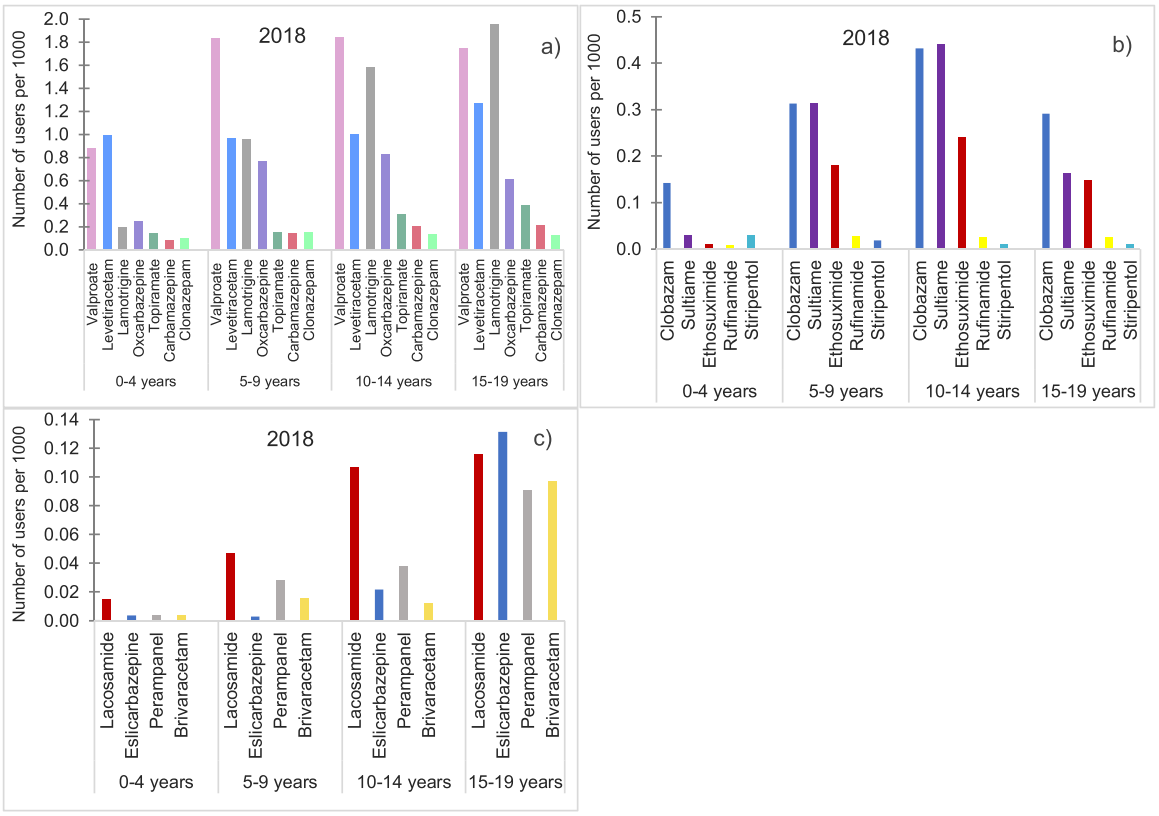

Fig. 2. a) The most commonly used ASMs in epilepsy in specific age groups in children and adolescents, as reflected by the numbers in 2018 (total number of users 0–19 years, n = 5119; 0–4 years: 520; 5–9 years: 1285; 10–14 years: 1612; 15–19 years: 1702 users). Vigabatrin, which is only used in infantile spasms, was only used in the youngest age group (0–4 years) (0.09/1000 users) and is not shown in the figure. b) The use of specific and special ASMs in epilepsy in specific age groups in children and adolescents, as reflected by the numbers from 2018 and c) The use of newer ASMs, defined as ASMs given authorization after 2008, in children and adolescents in 2018.

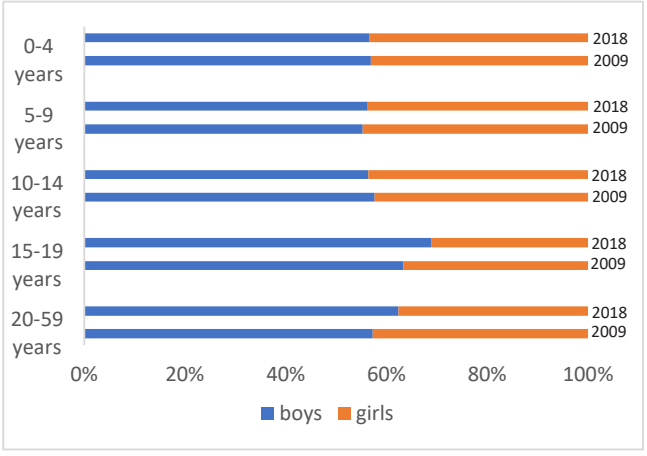

Fig. 3. Sex differences in the use of valproate in various age groups from children to adults in 2018 as compared to 2009.

ranging from 0.29 to 0.43/1000. During the whole period the use in boys was 20% higher than in girls, from 0.10/0.08 to 0.33/0.27 individuals per 1000 inhabitants.

The use of stiripentol was most prominent in the youngest children (0–4), whereas the use of sulthiame and ethosuximide was significantly lower in this group (Fig. 2b). The use of clobazam, sulthiame, and ethosuximide was highest in the groups aged 5–9 and 10–14 years.

In 2018 only about 1/3 of valproate users in epilepsy in the 15–19-year age group were girls (0.5 girls versus 1.2 boys (total 1.7) per 1000), but the proportion was relatively stable over the decade, at 31% of the total valproate use in epilepsy, and 37% in 2009 (Fig. 3). Only minor sex differences were seen in the younger age groups: girls accounted for 40–45% of the total valproate use in epilepsy in both 2009 and 2018. The use of valproate in epilepsy among adults, remained stable, where women accounted for 43% and 38% of the total valproate use in 2009 and 2018, respectively.

3.6. *Limited use of ASMs in non-epilepsy indications*

Limited and stable use of ASMs in non-epilepsy indications in the pediatric population was observed, accounting for 14–17% over the decade (Table 2). In 2018, the non-epilepsy indications constituted of < 10% of the use of ASMs in the youngest children (Number of users: 0–4 years: 32, 5–9 years: 89, 10–14 years: 203). In adolescents (15–19 years) an increase was seen and constituted 31% in 2018 (n = 697 users) versus 26% in 2009 (n = 596 users).

The use of ASMs in non-epilepsy indications was profoundly higher in adults: 71% of the total use in 2018 (n = 43.674 39.977 users), with a considerable increase over the decade (Table 2). In 2018, 69% of the non-epilepsy ASM use in adolescents was in psychiatry, 25% in neuropathic pain and 6% in migraine. Neuropathic pain was the main non-epilepsy indication in adults in 2018, comprising 55% of the total non-epilepsy use followed by psychiatric disorders (43%) and migraine (2%). Only a few ASMs were used in all age groups (0–19 years): Lamotrigine (n = 507) followed by valproate (n = 158) and carbamazepine (n = 17) in psychiatric disorders, gabapentin (n = 254), followed by pregabalin (n = 23) and carbamazepine (n = 14) in neuropathic pain, and topiramate in migraine (n = 46).

4. Discussion

The present findings demonstrate significant changes in the use of ASMs in the pediatric versus adult population in Norway over the last decade. For selected drugs such as ethosuximide, sulthiame and clobazam, the changes and extent of use were different among the younger age groups as compared to adults. Sex differences in use of valproate were seen, with a moderate change among adolescents and adults, in line with safety restrictions. The use of the most recently approved ASMs, as well as the use in non-epilepsy indications were limited in children/adolescents.

4.1. 1-Year prevalence and changes in the use of ASMs

The use of ASMs in children and adolescents remained stable and unchanged during the ten-year period regardless of indication. The 1-year prevalence of ASM use corresponds with previous population-based studies estimating active epilepsy in the pediatric populations in the Nordic countries (3.2–4.1 per 1000) and in Norway (0.39–0.47%, i.e., 3.9–4.7/1000) (Syvertsen et al., 2015; Aaberg et al., 2017). It should, however, be noted that up to 15% of children with a diagnosis of epilepsy do not use ASMs (Aaberg et al., 2016). The present results demonstrate that ASMs are used according to the main indication in children and adolescents, in line with similar studies (Baftiu et al., 2016; Karlsson Lind et al., 2018). For the adult population the use of ASMs in epilepsy also remained relatively unchanged. The 1-year prevalence was consistent with the prevalence of active epilepsy among adults (5.5 – 8.2/1000) (Syvertsen et al., 2015). However, the marked increase in use of ASMs in adults regardless of indication points to a further persistent increased utilization in non-epilepsy indications (Johannessen Landmark et al., 2009; Baftiu et al., 2016, 2018).

4.2. The most commonly prescribed ASMs in epilepsy

The trends in the use of ASMs in epilepsy in Norway have been relatively stable during the last decade. Valproate was more extensively used in children/adolescents than in the adult population. This was expected due to the frequent occurrence of generalized epilepsies in children, including absence epilepsy, and age-dependent epilepsy syndromes, where valproate as a broad-spectrum is a preferred ASM with a high level of evidence (Marson et al., 2007; Glauser et al., 2013). In young children with metabolic disorders there is an increased risk of hepatotoxicity, which is a rare but serious adverse effect (Star et al., 2014).

The use of valproate in young girls was not markedly different from boys, which assures equivalent treatment options between sexes in childhood. There was a shift towards more limited use in adolescents and women from childbearing age, as expected. However, valproate may still be the most efficacious ASM in some patients with generalized epilepsy (Tomson et al., 2015). A modest decrease in the use of valproate among adolescent girls was observed from 2009 to 2018, suggesting that treating physicians were restrictive in prescribing valproate to young women also before EMA's first restrictions in 2014. Recently, there were stronger safety restrictions due to teratogenicity and second-generation effects (Tomson et al., 2019). Focus on further surveillance of the use of valproate is thus important.

The most significant increase in use was seen with levetiracetam. Levetiracetam is an ASM which has shown efficacy in focal epilepsy and is also efficacious in myoclonus and other generalized epilepsies (Glauser et al., 2013; Weijenberg et al., 2015). A challenge in clinical practice is behavioral and psychological adverse effects (Weijenberg et al., 2015).

The use of lamotrigine has also been extensive in both children and adults over the decade. This ASM is efficacious in focal and generalized seizures and has also demonstrated mood-stabilizing effects in bipolar disorder (Glauser et al., 2013; Perucca and Mula, 2013). The use of lamotrigine increased with age, which is in line with a previous finding (Johannessen Landmark et al., 2011). In adolescents with epilepsy and psychiatric comorbidities, a rational choice of lamotrigine is often preferred (Karouni et al., 2010). The risk of severe skin rash is particularly high in children (Egunsola et al., 2015).

4.3. Extensive changes in the use of the selected ASMs

There was a marked increase in the use of clobazam in children, with epilepsy as the main indication. This is interesting, as clobazam is not classified as an ASM, but it is often used in children as well as in adults to treat refractory epilepsy, based on our clinical experience (Burns et al., 2016; Heger et al., 2020). Clobazam is a benzodiazepine with broad-spectrum effect against focal and generalized seizures, and has advantages compared to other benzodiazepines in terms of tolerability and tolerance, which may have contributed to its increasing use. In addition, the active metabolite provides a long duration of action (Brodie et al., 2016; Gauthier and Mattson, 2015). It has in recent years proven efficacious in treatment of refractory epilepsies as Lennox Gastaut and Dravet syndrome (Burns et al., 2016; Heger et al., 2020). Furthermore, there is a long tradition with using clobazam in epilepsy treatment in Norway. In the present study the use of clobazam as compared to clonazepam was more extensive in the pediatric population, while in adults it was opposite. In the UK, clobazam was more often prescribed than clonazepam, in both adults and children with epilepsy (Brodie et al., 2016). Due to extensive pharmacokinetic variability and many drug interactions close monitoring of clobazam and its active metabolite N-desmethyl clobazam is recommended (Burns et al., 2016).

An increase in the use of two other drugs was observed: ethosuximide and sulthiame (unlicensed in Norway). Ethosuximide is in guidelines recommended as first line treatment of absences, which is occurring often in children and adolescents, with an onset age of 4–10 years (Glauser et al., 2013; National Institute for Health and Care Excellence, 2012; Hirsch et al., 2021). This was reflected in the increased use of ethosuximide in these age groups in the present study. Likewise, the use of sulthiame increased in the age groups where the self-limiting focal childhood epilepsies presents, for which it is mainly used (5–14 years) (Specchio et al., 2021). Sulthiame is an old ASM and is not a first-hand choice in any seizure type (Glauser et al., 2013; National Institute for Health and Care Excellence, 2012). An increase in the use of stiripentol (1.5–2-fold) was seen from 2009 to 2010, then the use decreased and stabilized. Stiripentol was approved in Europe in 2007 and marketed in Norway in 2009. This indicates that many patients tried stiripentol following its approval, but it was then discontinued. Stiripentol is an orphan drug indicated in Dravet syndrome, a rare epilepsy syndrome with early onset (Wallace et al., 2016). Vigabatrin is used in infantile spasms and was therefore only used in the youngest children (Pesaturo et al., 2011).

The most recently approved ASMs will have a delay in use in children and adolescents, especially the youngest groups, due to the time before they are approved in these age groups following experience in adults. These drugs will first be approved as add-on treatment in focal seizures in adults, and then later in other epilepsies and age-groups. For example, lacosamide was approved in 2008 in patients $\geq$ 16 years as add-on in focal seizures. Extension of indication to include monotherapy and children aged 4 years and older was approved in 2016 and 2017, respectively (European Medicines Agency, 2021).

4.4. Limited use of ASMs in non-epilepsy indications

The present results demonstrate that the use of certain ASMs in non-epilepsy indications is stable and limited and constituted mainly of lamotrigine in psychiatry in adolescents (15–19 years). This was expected, as current evidence for the use of ASMs in non-epilepsy indications such as psychiatric disorders and migraine in young children is weak (Davico et al., 2018; Le et al., 2017). This contrasts with the

extensive use in adults, which has increased further over the years, based on our previous studies (Johannessen Landmark et al., 2011; Baftiu et al., 2016). No ASM is approved in psychiatric indications at the age below 18 years, and our results points to off-label use in adolescents and a limited number of younger patients. According to the warning for all ASMs in their product information, safety considerations and surveillance is important in the years to come, especially in adolescents who use ASMs outside approved indications.

4.5. Methodological considerations

NorPD is a validated and extensively used database that have been used in similar studies to explore changes in use of ASMs over time (Baftiu et al., 2016, 2018; Wettermark et al., 2013). Limitations of the database include that ASMs supplied and dispensed in hospitals, institutions and nursing homes are not included in the NorPD on the individual level. The total use of drugs may therefore be under-estimated. Also, adherence aspects cannot be controlled for in this database. Reimbursement codes from general and specialized healthcare are used and are not identical to codes for specific diagnoses. Also, one reimbursement code may cover several diagnoses, as in psychiatry. Previously, we have used the measure of defined daily doses (DDD), but this is not suitable as a variable to express the extent of use in children, as it is defined as use for the main indication in adults (WHO Collaborating Centre for Drug Statistics Methodology, 2018). Therefore, it was not used in the present study, which could make direct comparisons to previous studies more complicated. The elderly were excluded from further analysis. It was not considered relevant for comparison with children and adolescents regarding extent of use, preferences of the various ASMs, and occurrence of different epilepsy types/syndromes/etiologies. Details of this age group have been described in a previous study (Baftiu et al., 2018). The 1-year prevalence for non-epilepsy indications was calculated by summarizing the use of ASMs in migraine, neuropathic pain, and psychiatric indications. When subtracting 1-year prevalence for epilepsy use from 1-year prevalence for total use, there is about 10% discrepancy from total non-epilepsy use (Table 2). This can be attributed to the fact that some patients may have received the same ASM for different indications, or that some patients use several ASMs in both epilepsy and in other indications. To gain further knowledge of safety measures, there is a need to investigate trends and changes in the use of drugs at the population level to identify drugs to study in more detail in subgroups of patients.

5. Conclusions

This study demonstrates similar prescription patterns of the most common ASMs in children/adolescents as compared to adults. In contrast, there were major differences among the selected ASMs, where the extent and increased use of e.g., ethosuximide, sulthiame and clobazam was more prominent in the younger age groups than in adults, and the most recently approved ASMs was limited in children. Clobazam was predominantly used in epilepsy. The use of valproate in adolescent girls was restrictive with moderate changes over the last decade The use of ASMs in non-epilepsy indications is limited in children and adolescents, in contrast to the wide non-epilepsy use in adults. The NorPD enables surveillance of special patient groups, as children and adolescents, as well as new and special ASMs, as part of pharmacovigilance and patient safety evaluations.

Author statement

C. Johannessen Landmark and S. Skurtveit planned the study. The collection of data was performed by S. Skurtveit at the Norwegian Institute of Public Health. Further handling and analyses of the data were performed by K. Heger and J. Skipsfjord. Interpretation and clinical evaluation of the data were done by all authors. K. Heger and C. Johannessen Landmark wrote the first draft of the manuscript. All authors were involved in the process and evolution of the manuscript to its final approval by everyone. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declarations of interest

None.

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