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ORIGINAL ARTICLE

Medical treatment in infants and young children with epilepsy: Off-label use of antiseizure medications. Survey Report of ILAE Task Force Medical Therapies in Children

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Abstract

Objective: Antiseizure medications (ASMs) remain the mainstay of epilepsy treatment. These ASMs have mainly been tested in trials in adults with epilepsy, which subsequently led to market authorization (MA). For treatment of – *especially young* – children with epilepsy, several ASMs do not have a MA and guidelines are lacking, subsequently leading to "off-label" use of ASMs. Even though "off-label" ASM prescriptions for children could lead to more adverse events, it can be clinically appropriate and rational if the benefits outweigh the risks. This could be the case if "on-label" ASM, in mono- or polytherapy, fails to achieve adequate seizure control.

Methods: The Medical Therapies Task Force of the International League Against Epilepsy (ILAE) Commission for Pediatrics performed a survey to study

the current treatment practices in six classic, early life epilepsy scenarios. Our aim was not only to study first- and second-line treatment preferences but also to illustrate the use of "off-label" drugs in childhood epilepsies.

Results: Our results reveal that several ASMs (e.g. topiramate, oxcarbazepine, benzodiazepines) are prescribed "off-label" in distinct scenarios of young children with epilepsy. In addition, recent scientific guidelines were not always adopted by several survey respondents, suggesting a potential knowledge gap.

Significance: We report the relatively common use of "off-label" prescriptions that underlines the need for targeted and appropriately designed clinical trials, including younger patients, which will also result in the ability to generate evidence-based guidelines.

KEYWORDS

children, epilepsy treatment, International League Against Epilepsy, off-label, questionnaire

1 | INTRODUCTION

Epilepsy is one of the most common neurological diseases worldwide, with over 10 million children affected by this disease.[1] The target of epilepsy treatment is to achieve seizure control with antiseizure medications (ASMs). These drugs modulate different pathways and subsequently decrease neuronal excitation and/or increase neuronal inhibition. The first ASM to be used was phenobarbital in 1912. Subsequently, ASM development increased exponentially in the past 30 years leading to over 25 ASMs being registered.[2,3] Novel ASMs have led to more tailored treatment choices to the individual's characteristics, although they have not significantly reduced the number of patients with drug-resistant epilepsy.[3] For example, up to 28% of children with epilepsy have insufficient control of their seizures managed with the currently available ASMs due to the lack of efficacy and/or tolerability issues.[1,4] The heterogeneity of response to the existing ASMs underlines the high need for tailored treatment options. Due to our increasing understanding of the pathogenesis of epilepsy, we are able to choose/avoid specific ASMs in certain cases. This constellation is especially true for monogenic epilepsy syndromes for which individualized medicine approaches are possible (e.g. everolimus for tuberous sclerosis complex [TSC]).[5]

While regulatory incentives have been promoted to stimulate pediatric trials by pharmaceutical companies, therapeutic options for pediatric epilepsies remain relatively scarce. Numerous pediatric epilepsy syndromes are still not considered for ASM development trials *or* do not include young children,[6] and/or the ASM is only marketed as add-on therapy for older pediatric and adult populations,[7] which results in the "off-label" prescription of ASMs by child neurologists worldwide. Hence, there remains an unmet need for studies on (younger) children with epilepsy.

Key Points

- Epilepsy treatment usually involves antiseizure medications (ASMs) that have been mainly tested in adult clinical trials.
- The lack of proper guidelines and clinical trials in – *especially very young* – children with epilepsy leads to the "off-label" use of ASMs.
- Our survey shows that several ASMs are prescribed "off-label", especially in the very young children with epilepsy.
- Including younger age groups in trials of ASMs would lead to evidence-based guidelines and a reduction of "off-label" ASM use.

"Off-label" refers to the use of a drug beyond the market authorization (MA) specifications in terms of age, indication, categories of patients, pharmaceutical form and dose frequency/regimen.[1,8,9] Some research has shown a clear correlation between the "off-label" drug use and adverse drug reactions,[10] e.g. leading to an adverse drug reaction increase of 33%[11] or 70%.[12] However, in a recent joint position statement,[13] the European Academy of Pediatrics (EAP) and the European Society for Developmental Perinatal and Pediatric Pharmacology (ESDPPP) have recommended that "off-label" drug prescription can be rational and clinically appropriate for children if the benefits outweigh the risks. In addition, the World Health

Organization (WHO) launched a campaign named "make medicines child size", in which they share the same aims as the EU regulation: "to improve availability of age-appropriate medicines for children, to make information available and to increase high-quality ethical research, without conducting unnecessary trials in children".[1,14] The European Medicines Agency (EMA) and the Food and Drug Administration (FDA) have provided a framework to extrapolate the efficacy results of drug trials from adults to children. This extrapolation is defined as "extending information and conclusions available from studies in one or more subgroups of the patient population (source population[s]), or in related conditions or with related medicinal products, in order to make inferences for another subgroup of the population (target population), or condition or product, thus reducing the amount of, or general need for, additional information (types of studies, design modifications, number of patients required) needed to reach conclusions". These ambitions should lead to an increase of "on-label" ASMs for the pediatric population[1] and could be stimulated by pharmaceutical companies focusing on one or more subgroups of a patient population. In return, the companies can obtain several incentives, e.g. exclusive marketing and patent extension to test medications in children.[15]

To investigate the occurrence of "off-label" ASM use, we analyzed the prescription behavior of over 500 neurologists worldwide in six different epilepsy scenarios in infants and young children.

2 | MATERIALS AND METHODS

On behalf of the Medical Therapies Task Force of the ILAE Commission for Pediatrics, we constructed a survey and distributed this to (pediatric) neurologists with an interest in pediatric epilepsy (i.e. patients with epilepsy from 0-18 years of age). Pediatric neurologists were defined as medical doctors who are treating children with epilepsy below 18 years of age.

In August 2020, the survey was distributed worldwide using the channels of ILAE, International Child Neurology Association (ICNA), European Pediatric Neurology Society (EPNS) and Asian and Oceanian Child Neurology Association (AOCN) to reach as many respondents as possible.

In total, the questionnaire contained 27 questions (see Appendix S1). The first seven questions concerned general (demographic) information and the current situation of clinical practice. Subsequently, 20 different questions followed involving medical treatment options in six distinct cases: (a) neonatal seizures, (b) febrile seizures, (c) TSC, (d) focal seizures, non-structural, (e) infantile epileptic spasms, and (f) Dravet syndrome. The questionnaire contained mostly open-ended questions for which only one answer was allowed, although one question allowed multiple answers (i.e. concerning the intervention for febrile seizures). For the ASMs, generic names were used. The aims were (a) to understand first- and second-line use in the six typical scenarios and (b) to illustrate the use of "off-label" drugs in childhood epilepsies. Overall, no statistics were used for this study and figures were made by Microsoft Excel 16.16.27 for the scenarios with questions regarding first- and second-line ASM, i.e. scenarios 3, 4, 5 and 6.

3 | RESULTS

3.1 | General information

A total of 515 people responded to the survey. The majority of the respondents (343/515, 66.6%) were pediatric neurologists. Others included adult neurologists, pediatric/adult epileptologists, residents/fellows in (pediatric) neurology/epilepsy, pediatricians or general practitioners involved in epilepsy care (Table S1). About 71.3% (367/515) obtained training in an Epilepsy Unit for at least 6 months and more than half of the respondents (299/515; 58.1%) had more than 10 years of practice in epilepsy care. Nearly 54% (278/515) of the respondents were practicing in Europe and Central Asia (Figure S1). Although we reached out to respondents in Africa and South America as well, only very few clinicians did reply and completed the survey. These respondents were practicing in Japan (96/515; 18.6%), Spain (63/515; 12.2%), USA (35/515; 6.8%), UK (32/515; 6.2%), France (14/515; 2.7%), Italy (12/515; 2.3%), the Netherlands (12/515; 2.3%), Croatia (11/515; 2.1%), Hungary (11/515; 2.1%), India (10/515; 1.9%), Switzerland (10/515; 1.9%), and Zimbabwe (10/515; 1.9%). For the other countries, less than 10 respondents were noted (Table S2).

About 68.5% (353/515) of the respondents were active at a University/Academia or teaching hospital/Tertiary Referral center. One hundred and nineteen respondents (119/515; 23.1%) were practicing at a regional non-academic hospital and 27/515 (5.2%) were active at a private clinic. More than half of the respondents (312/515; 60.6%) indicated that they were based in a setting where limited resources would not affect their decisions in this survey.

3.2 | Scenarios

3.2.1 | Neonatal seizure follow-up

A 6-week-old boy with a prior history of hypoxic ischemic encephalopathy at birth, Apgar 1, 2, 6, is seen for

follow-up. He presented with frequent clinical and electrographic seizures on the first day of life and was treated initially with phenobarbital (PB), without seizure control, so levetiracetam (LEV) was added. He became seizure free on day 4. EEG performed prior to discharge revealed generalized background slowing and brain MRI showed bilateral basal ganglia and thalamus hyperintensity on T1, T2, and FLAIR with diffusion restriction, consistent with hypoxic–ischemic injury. At follow-up, he remains on both medications and still is seizure free. Neurologic examination shows mild hypotonia and poor visual tracking.

Most of the respondents would repeat the EEG (317/467; 67.9%). One out of four respondents would repeat the MRI (120/467; 25.7%). Regarding medical management, about half of the respondents (219/467; 46.9%) were in favor of continuing levetiracetam for a longer time. As shown in Table 1, 36.6% (34.9% + 1.7%) respondents wanted to taper both drugs (one after the other or both at once, respectively). About half of the respondents (181/393; 46%) would use the ASMs for less than 6 months. The others would use them for 6-12 months (110/393; 28%), 1-2 years (58/393; 14.8%) or longer than 2 years (44/393; 11.2%).

3.2.2 | Febrile seizures

A 14-month-old child with normal development presents with a history of three short lasting, self-limited bilateral tonic–clonic febrile seizures, which occurred as isolated events during febrile illnesses at the ages of 6, 8 and 13 months. Parents ask whether medication is necessary and if so, what drug you would prescribe?

Sixty-two of the respondents skipped this question, leading to 453 responses. Most of the respondents (268/453; 59.2%) would use rescue therapy with a benzodiazepine to be given only for febrile seizures lasting longer than 5 minutes. One out of 10 respondents (45/453; 9.9%) would start prophylactic ASM treatment at the start of each febrile illness. The majority of these respondents were from Asia (30/45; 66.7% [Japan: 25/45; 55.6%]), were pediatric neurologists/epileptologists (34/45; 75.6%), had more than 10 years of experience (28/45; 62.2%), were situated at a University/Academia or teaching hospital/Tertiary Referral center (28/45; 62.2%) and would start diazepam suppository or gel as an ASM (31/35; 88.6%; *only 35 responses for this question*).

About one fifth of the respondents (86/453; 19%) would start antipyretic medication to specifically reduce the risk of febrile seizures. Only the minority (19/453; 4.2%) would start regular/chronic ASM treatment. In contrast, 43.3% (196/453) would not use any ASMs, would reassure parents and discuss when to seek emergency care. The reported ASMs (regular/chronic/prophylactic) were sodium valproate (9/48; 18.8%), levetiracetam (2/48; 4.2%), carbamazepine (1/48; 2%), and perampanel (1/48; 2%). Other drugs that were used were diazepam (31/48; 64.6%), clobazam (3/48; 6.3%), and clonazepam (1/48; 2%).

TABLE 1 Treatment strategy (case 1 neonatal seizures)

Total	100%	*N* = 467
Continue LEV monotherapy for a longer time	46.9%	219
Continue PB monotherapy for a longer time	3.4%	16
Continue both drugs for a longer time	13.1%	61
Taper both drugs now (taper one after the other)	34.9%	163
Taper both drugs now (taper both at once)	1.7%	8

Abbreviations: LEV, levetiracetam; PB, phenobarbital.

3.2.3 | Tuberous sclerosis complex

A 2-year-old child with TSC, diagnosed after antenatal detection of cardiac rhabdomyomas and MRI confirming cortical tubers, presents with frequent events characterized by quietening of activity, fearful expression and cyanosis. These events had been noted for 2 months, but not recognized as seizures. The child has mild motor and speech impairments. A video EEG showed multifocal epileptic discharges interictally and captured these events, confirming they are focal onset seizures. Which first-line ASM would you use?

Seventy-five of the respondents skipped this question, leading to 440 responses. Most respondents chose vigabatrin, levetiracetam, carbamazepine, oxcarbazepine or sodium valproate (Figure 1A).

If seizures continued during the next 4 weeks, most respondents (256/440; 58.2%) would add a second ASM to the first ASM. The remainder (184/440; 41.8%) would try a second ASM in monotherapy (weaning the first drug whilst increasing the second drug). Most of these respondents selected levetiracetam, sodium valproate, vigabatrin oxcarbazepine, carbamazepine, lamotrigine, clobazam, topiramate, lacosamide, or everolimus as second line (Figure 1B). The second-line ASMs which were chosen for the two most common first-line ASMs (vigabatrin and levetiracetam) are shown in the Figures S2 and S3.

3.2.4 | Focal seizures, non-structural

A 6-month-old developmentally normal female infant presents with high frequency of afebrile focal to bilateral

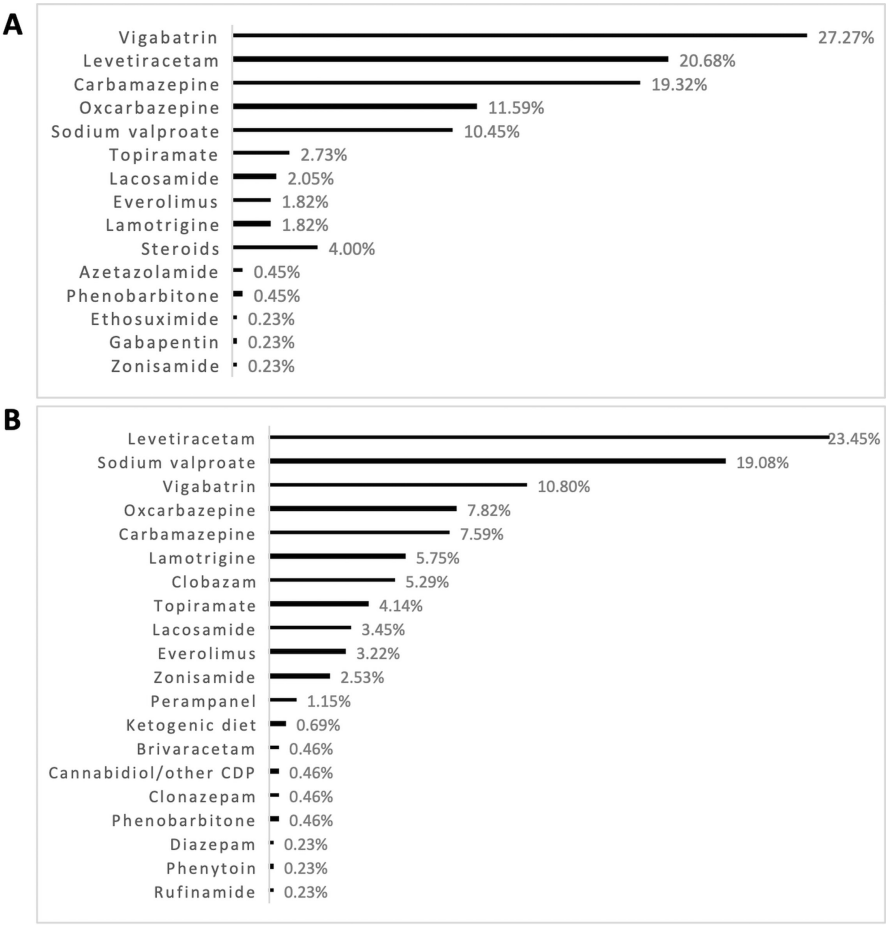

FIGURE 1 Case 3 tuberous sclerosis complex. (A) First antiseizure medication ($n = 440$, 100%); (B) second antiseizure medication if seizures would continue during the next 4 weeks ($n = 435$, 100%). CDP, cannabis derived products; steroids, e.g. cortisone or ACTH.

tonic–clonic seizures, with five seizures seen within the last 48 hours. Her neurological examination is normal. Her mother had a history of seizures as an infant that remitted with age. There is no family history of developmental or learning disorders. MRI and interictal EEG (which includes sleep) are normal. Which first-line ASM would you use?

Eighty-five of the respondents skipped this question, leading to 430 responses. Most respondents chose levetiracetam, carbamazepine, sodium valproate, oxcarbazepine or phenobarbital (Figure 2A).

If seizures continued during the next 4 weeks, one third of the respondents (153/431; 35.5%) would add a second ASM to the first ASM. Most respondents (278/431; 64.5%) would try a second ASM in monotherapy (weaning the first drug while increasing the second drug). Most of these respondents chose levetiracetam, sodium valproate, carbamazepine oxcarbazepine, lamotrigine, topiramate, clobazam, lacosamide or zonisamide as second line (Figure 2B).

We also analyzed which drug was chosen as second-line ASM. We studied these second-line ASMs when the first-line ASM was levetiracetam (Figure S4) and when the first-line ASM was carbamazepine (Figure S5).

3.2.5 | Epileptic spasms

A 6-month-old boy has definite epileptic spasms commencing 2 weeks prior to presentation. EEG confirms epileptic spasms and hypsarrhythmia. There is also developmental regression/stagnation since the start of the spasms. No MRI is available yet. Assuming that the child has no features of TSC, what is your first treatment choice?

Eighty-eight of the respondents skipped this question, leading to 427 responses. Most respondents chose ACTH or oral steroids, vigabatrin, sodium valproate or pyridoxine. The combination of vigabatrin and ACTH/steroids was proposed by 20% of the respondents (Figure 3A).

Follow-up scenario 1 (Epileptic spasms)

The MRI reveals periventricular leukomalacia, the patient has fewer epileptic spasms 2 weeks after your first treatment choice commenced and has not regained prior developmental ability. An EEG recorded a few epileptic spasms. The background is abnormal, but is not hypsarrhythmic anymore.

Over half of the respondents (217/427; 50.8%) would continue the same treatment during the next 2 weeks. The

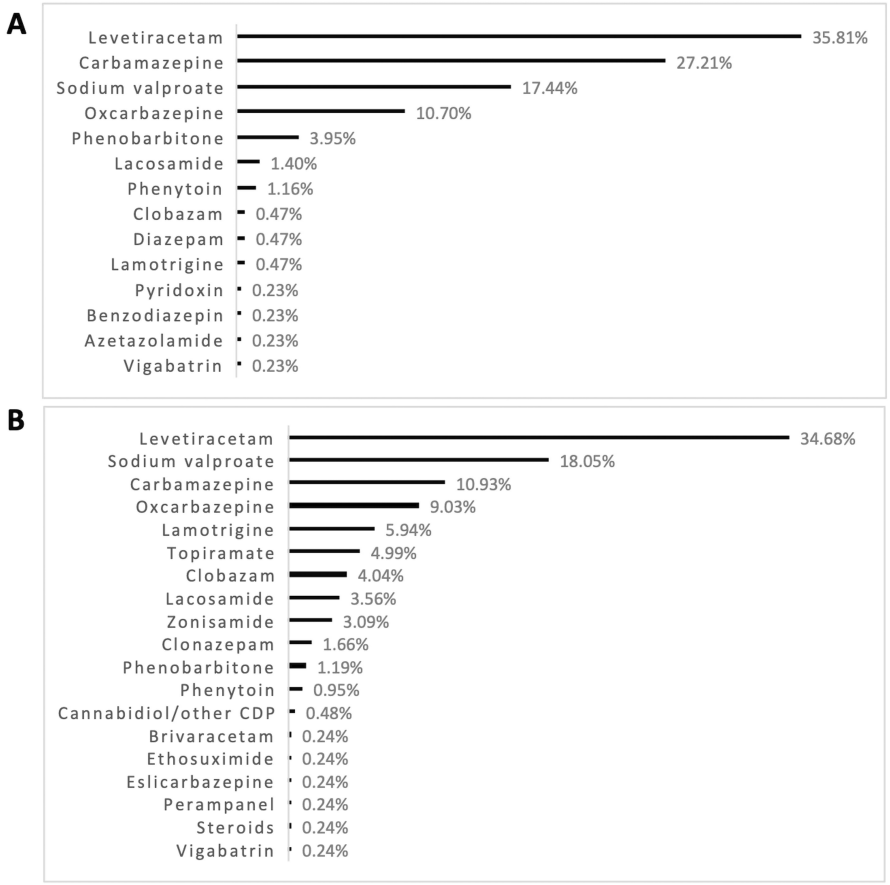

FIGURE 2 Case 4 focal seizures, non-structural. (A) First antiseizure medication (n = 430, 100%); (B) second antiseizure medication if seizures would continue during the next 4 weeks (n = 421, 100%). CDP, cannabis derived products; steroids, e.g. cortisone or ACTH.

other half (210/427; 49.2%) would add or switch to another treatment option.

Three hundred of the respondents skipped the question regarding second ASM treatment, leading to 215 responses. For second line in this follow-up scenario 1, most respondents chose vigabatrin, ACTH or oral steroids, sodium valproate, topiramate, levetiracetam, zonisamide or clobazam (Figure 3B).

Follow-up scenario 2 (Epileptic spasms)

The MRI is normal, the patient has fewer epileptic spasms 2 weeks after starting the first treatment and developmental skills he had before the start of spasms have returned. An EEG recorded no epileptic spasms. The background remains abnormal but is not hypsarrhythmic anymore.

Over half of the respondents (247/423; 58.4%) would continue the same treatment during the next 2 weeks. One out of four respondents (107/423; 25.3%) would add or switch to another treatment option. The same drugs were preferred for second-line treatment: sodium valproate, vigabatrin, ACTH or oral steroids, levetiracetam, topiramate, zonisamide or clobazam (Figure 3C). The remaining respondents (69/423; 16.3%) would stop the first treatment.

3.2.6 | Dravet syndrome

A 15-month girl is admitted after a short lasting (2 minutes) generalized tonic clonic seizure without fever. She was recently diagnosed with Dravet syndrome (DS), after having had unilateral prolonged (both > 7 minutes) seizures at the ages of 8 and 13 months, both in periods of fever and illness. Which first-line ASM would you use?

One hundred and three of the respondents skipped this question, leading to 412 responses. Most respondents chose sodium valproate, levetiracetam, stiripentol or clobazam (Figure 4A). Sodium valproate was the preferred first-line drug for 74% of the respondents.

If seizures continued during the next 4 weeks, most of the respondents (371/415; 89.4%) would add a second ASM to the first ASM. The remainder (44/415; 10.6%) would try a second ASM in monotherapy (weaning the first drug whilst increasing the second drug). Most of these respondents chose clobazam, stiripentol, topiramate, sodium valproate, levetiracetam, clonazepam or cannabidiol (Figure 4B), with a clear preference for clobazam (44%). The second ASMs that were chosen for the two most common first-line ASM (sodium valproate and levetiracetam) are shown in the Figures S6 and S7.

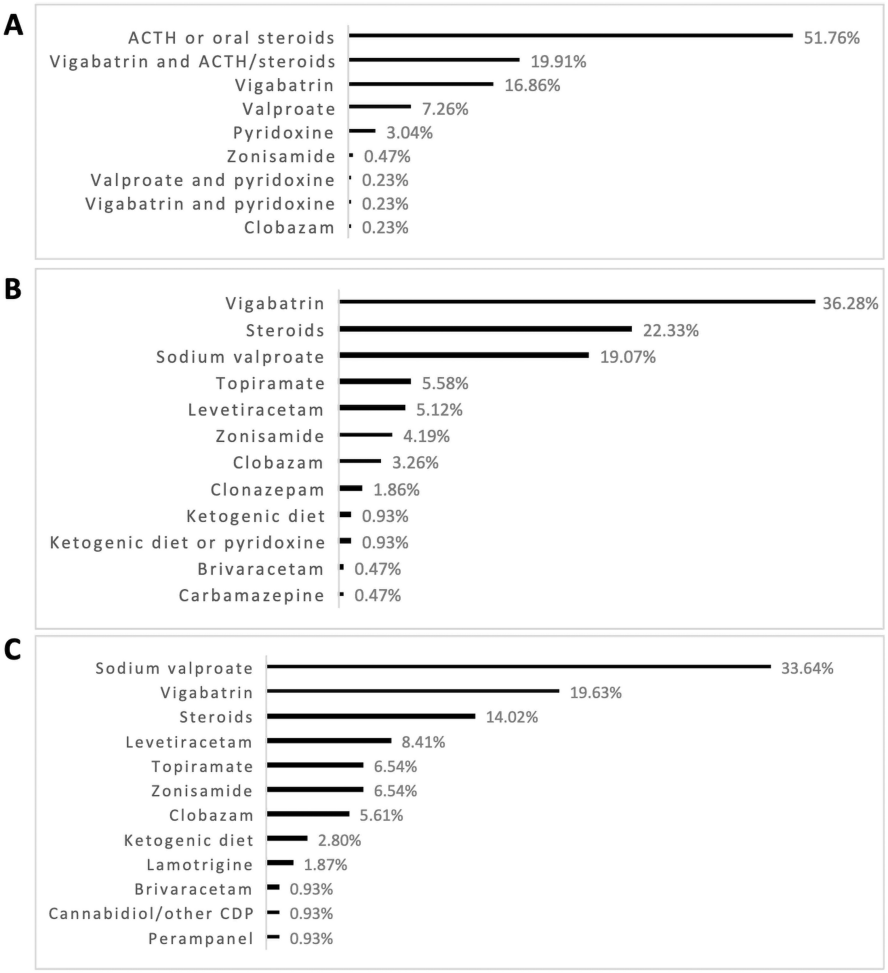

FIGURE 3 Case 5 epileptic spasms. (A) First antiseizure medication (n = 427, 100%); (B) second antiseizure medication scenario 1 (n = 215, 100%); (C) second antiseizure medication scenario 2 (n = 107, 100%). CDP, cannabis derived products; steroids, e.g. cortisone or ACTH.

4 | DISCUSSION

In children with epilepsy, an appropriately chosen ASM in monotherapy is the preferred treatment approach. If monotherapy trials of two ASMs fail, add-on treatment is usually offered to the patient. In 2010, the ILAE proposed the definition of drug-resistant epilepsy as "failure of adequate trials of two tolerated, appropriately chosen and used ASM schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom".[16] Since more than 30% of the patients with epilepsy have drug-resistant epilepsy, clinicians worldwide are hampered in finding the best treatment option for their patients.[1]

One of the goals of the Medical Therapies in Children Task Force of the ILAE Commission for Pediatrics (2017-2021) was to better understand treatment options in young children with epilepsy. Especially in infants and young children, randomized controlled trials (RCTs) remain scarce and in many cases "off-label" use of ASMs is current clinical practice. The existing guidelines on best treatment options for many of these early-onset epilepsies do not take into account that some of the proposed drug treatments are "off-label". Within the Task Force we constructed this short survey focusing on six "typical" clinical scenarios. The herein presented scenarios illustrate that "off-label" drugs in childhood epilepsies are sometimes chosen as first- and second-line treatment preferences.

Overall, we did not encounter major deviations from what is known based on literature data and/or guidelines. This is most likely due to the apparent high level of clinical experience in majority of the respondents, which could be a bias to our study. Since our survey was completed by several health care providers worldwide, stratification of the answers by demographics of the respondents could unravel regional differences. However, this was beyond the scope of our study but should be included in future studies with a preset power and sample size estimation to allow statistically substantiated results and conclusions.

With regard to the neonatal seizure follow-up, most respondents chose to continue levetiracetam for less than 6 months (46.9%) for the treatment of (symptomatic) neonatal seizures (*scenario 1*). In this patient, phenobarbital was initially started as it is recommended and common clinical practice.

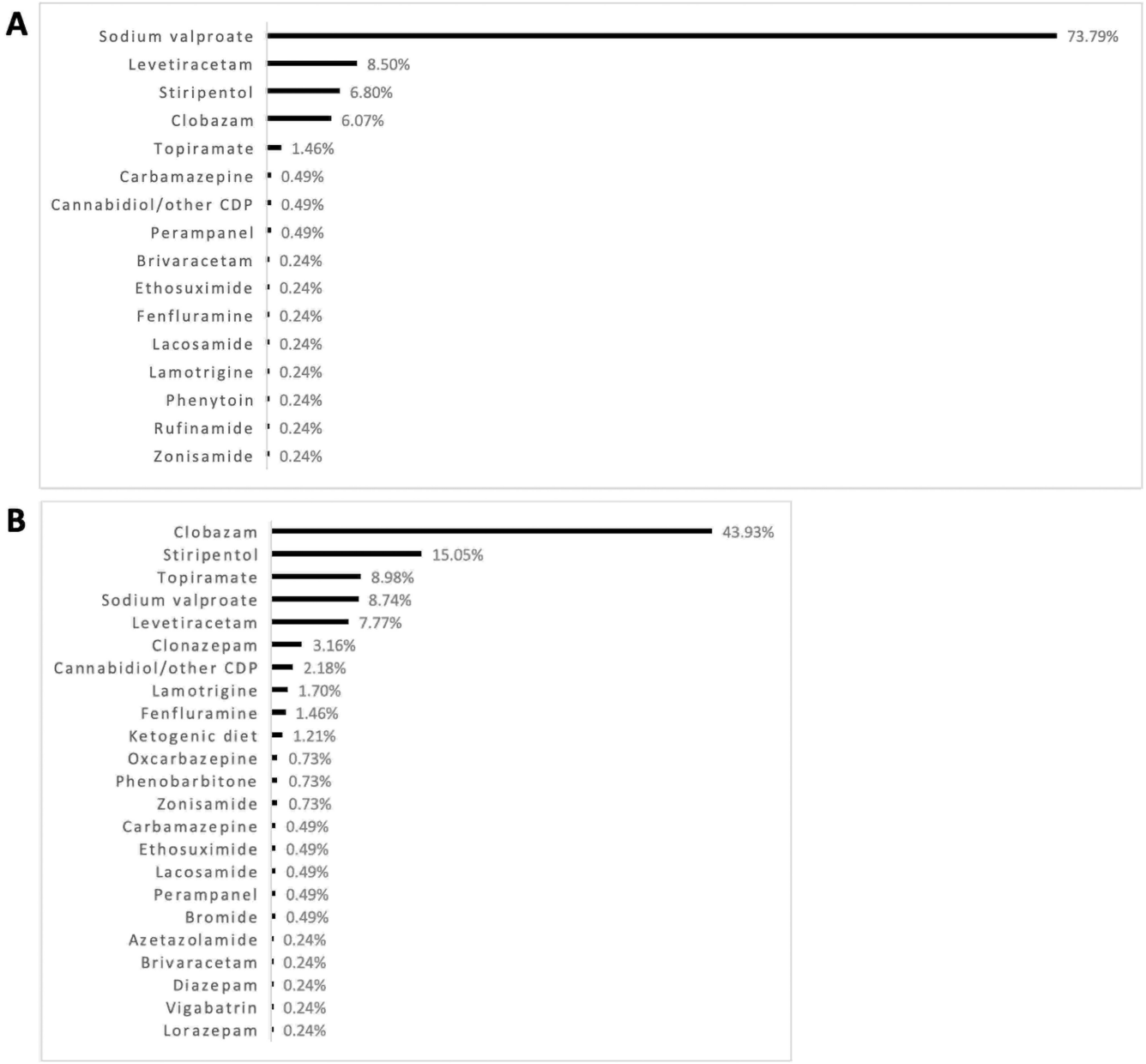

FIGURE 4 Case 6 Dravet syndrome. (A) First antiseizure medication (n = 412, 100%); (B) second antiseizure medication (n = 412, 100%). CDP, cannabis derived products; steroids, e.g. cortisone or ACTH.

More recently, many centers have started to favor levetiracetam as first- or second-line ASM in neonatal seizures due to its favorable pharmacokinetics and excellent tolerability.[17–20] In addition, preclinical studies have led to concerns about safety of phenobarbital[20,21] as well as its efficacy in the neonatal period.[22,23] However, a recent RCT comparing phenobarbital vs. levetiracetam has provided first class evidence that phenobarbital is the most effective ASM in this age group: the primary outcome measure (seizure control at 24 hours) was achieved in 24/30 neonates in the phenobarbital group vs. only 15/53 neonates in the levetiracetam group (RR 0.35, CI: 0.22, 0.56). Although more adverse effects occurred in the phenobarbital group, the difference was not significant. Thus, there is no evidence from (prospective) RCTs that levetiracetam is as effective or safer than phenobarbital.[24]

Levetiracetam is approved for the treatment of focal seizures from 1 month of age onwards. Hence, it is not surprising that the majority of respondents would switch to levetiracetam monotherapy (46.9%). On the other hand, there is an ongoing controversy regarding the duration of treatment after acute provoked seizures. In fact, a recent study (*published after the survey*) of 303 children from nine centers with neonatal seizures comparing those in whom the ASMs were maintained at hospital discharge after neonatal seizures resolved vs. those where the ASMs were

discontinued, did not show any difference in epilepsy or functional neurodevelopment at 2 years of age between these two groups.[25] Even early withdrawal of phenobarbital after 12 hours of seizure freedom is not associated with a higher risk of seizure recurrence.[26] In our survey, most respondents (83.5%) would limit the treatment to 6 months (46.9%) or would taper one or both (one after the other) ASMs immediately (36.6%). However, new evidence suggests that in neonates with acute provoked seizures who respond to initial treatment, ASM should be stopped before discharge from the neonatal unit.[27]

A recent ILAE paper provides clear guidance on the classification of neonatal seizures.[28] Regarding the treatment, however, the ILAE Neonatal Seizure Guideline Task Force is updating the World Health Organization (WHO) guidelines of 2011.[29]

Hence, phenobarbital remains the first line of treatment, although levetiracetam is an attractive alternative. The ASM choice in the management of neonatal seizures is based on the consensus of local experts.[30,31]

In the case of febrile seizures (*scenario 2*), most respondents (59.2%) would use rescue benzodiazepine therapy to be given only if seizures are longer than 5 minutes. Together with the large group who would reassure parents and discuss when to seek emergency care, 86% would not start any regular ASM. This finding is consistent with the fact that continuous ASMs for the prevention of febrile seizures or intermittent ASM usage is not recommended,[32] underlining the self-limiting nature of the phenomenon. Of interest, nearly one out five respondents (86/453; 19%) would start antipyretic medication to specifically reduce the febrile seizures risk even though antipyretics have no proven preventive role in febrile seizures.[33] Furthermore, almost 10% indicated they would start prophylactic ASM treatment at fever of which 55.6% of the respondents were from Japan. This finding is not surprising since the guidelines in Japan have only recently changed, now recommending not to utilize prophylactic ASMs, and our findings indicate that they have likely not been taken up by all providers.[34]

Based on the published guidelines by the ILAE from 2009,[35] combined with the current knowledge,[32,33] it is recommended not to start (regular) ASM and educate the parents/caregivers about febrile seizures and when to administer rescue benzodiazepine therapy.

For the 2-year-old patient with TSC (*scenario 3*), presenting with focal seizures, most chose vigabatrin (27.3%). This is a relatively low percentage considering vigabatrin, although it is the first choice for the treatment of seizures in TSC patients, also when focal seizures occur.[36] The other respondents preferred levetiracetam, carbamazepine and oxcarbazepine, following recent guidelines.[36] Interestingly, oxcarbazepine, which was chosen by one out of six of the respondents, is only approved in children older than four or even 6 years of age in most countries (vs. 2 years of age in the USA), thus used "off-label". Even though no consensus regarding the start of a second-line ASM is present, the relatively high occurrence (60% of the respondents in our survey) of add-on treatment is probably linked to the diagnosis of TSC, which frequently results in treatment-resistant seizures.[37] Nearly, one out of five would use sodium valproate (19.1%; second most chosen ASM) as second-line ASM.

Based on the recent literature, vigabatrin is recommended for the initial treatment of TSC-related seizures, even if they are focal of origin.[36] The use of second-line ASM for TSC-associated seizures should follow that of other epilepsies. Even though everolimus and cannabidiol formulation are approved by regulatory authorities, there are no comparative effectiveness data to recommend certain ASM over one another in a specific subset of TSC patients.[38]

For the treatment of (non-structural) focal seizures in a 6-month-old infant (*scenario 4*), levetiracetam was most frequently chosen (35.8%). This is an expected finding since it is an EMA- and FDA-approved for the treatment of focal epilepsy in children from 1 month of age.[39,40] The second most chosen ASM was carbamazepine (27.2%), while less than 18% would use sodium valproate. In line with these findings, a meta-analysis, involving children and adults, previously found that carbamazepine was more effective compared to sodium valproate as first-line ASM for focal seizures. With regards to the "off-label" use, over one out of 10 respondents (10.7%) chose oxcarbazepine, despite that this ASM is not approved at this age.

Based on the aforementioned literature and National Institute for Health and Clinical Excellence (NICE) guidelines, levetiracetam is recommended as first-line monotherapy for focal seizures. If the first choice is unsuccessful, other ASMs include lamotrigine, carbamazepine, oxcarbazepine and zonisamide; although these treatment options are not approved for the treatment of focal seizures in the (very) young.[41]

The treatment of epileptic spasms in an infant (*scenario 5*) should include ACTH or steroid therapy combined with vigabatrin, since this combination treatment is more effective than either of the drugs alone, according to the International Collaborative Infantile Spasms Study (ICISS).[42] Only in cases of TSC, isolated administration of vigabatrin is the preferred treatment.[43] Therefore, the results of our survey were surprising since more than 80% did not select the aforementioned combination treatment option. Moreover, following the United Kingdom Infantile Spasms Study (UKISS), one should assess the efficacy of treatment within 2 weeks and change the treatment strategy if no improvement is noted since there is a significantly

increased risk for drug-resistance when seizures remain uncontrolled for over 2 weeks.[44] However, half of the respondents (49.2%) would add or switch to another treatment regimen in our survey. Notwithstanding the above, there are no studies available regarding the preferred ASM to use after the failure of first-line drugs (ACTH or steroids and/or vigabatrin).

Therefore, combination treatment with oral steroids and vigabatrin as first-line therapy for infantile spasms is recommended. If the child has TSC or is at relatively high risk of steroid-related side effects, vigabatrin alone treatment should be considered.[41]

Sodium valproate and clobazam are first-line ASMs for Dravet syndrome (*scenario 6*) patients.[45] Accordingly, our survey shows that nearly three out of four respondents (73.8%) would start sodium valproate treatment. This finding is in line with recently published treatment protocols,[45–47] indicating that Dravet syndrome treatment practice is relatively consistent in several clinical centers.

Initial treatment with clobazam was suggested by 6.1% of the respondents. If one is concerned to use sodium valproate in the very young, clobazam could be an alternative ASM in line with the American guidelines.[45,46] The second most chosen ASM was levetiracetam (8.5%), even though this is proposed as a third-line ASM by many guidelines.[45] Nearly 7% of the respondents (6.8%) would use stiripentol as first line, but this ASM is not available in all countries.

Clobazam was added by 43.9% of the respondents to the treatment regimen when seizures were not controlled. Stiripentol or topiramate was prescribed as second line by 15.1% and 9.0% of the respondents, respectively. Topiramate was chosen as first-line (1.5%) or second-line ASM (9.0%), though this drug is also not approved for treating Dravet syndrome patients under the age of 2 years.[48,49] Our survey shows that stiripentol and topiramate are prescribed "off-label", especially in very young patients. In addition, clobazam has no MA as an ASM in many countries.

The aforementioned literature and NICE guidelines advise sodium valproate as first-line treatment, partially due to the paucity of data for other effective first-line ASMs.[41] If sodium valproate alone is unsuccessful; triple therapy with stiripentol and clobazam, or topiramate, or ketogenic diet should be considered. From 2 years of age onwards cannabidiol or fenfluramine can also be considered as second-line ASM.[50,51] Since the therapeutic landscape of Dravet syndrome is expanding, we must underline that the current treatment recommendations can alter over time. As such, add-on treatment options for Dravet syndrome currently include stiripentol, levetiracetam, fenfluramine, and cannabidiol.[52] Moreover, genetic therapies are being developed and clinical trials are currently ongoing to evaluate their potential in Dravet syndrome treatment.[53]

5 | CONCLUSION

The purpose of this study was to investigate the occurrence of "off-label" use of ASM in the pediatric population. Our study included a survey of six typical early onset epilepsy scenarios. Although the results are mainly confirmatory with treatment options following national and international guidelines, some minor deviations were noted. Not all respondents were aware of recent guidelines and some guidelines/studies were only available after the survey was circulated. This was especially the case for febrile seizures, but also for the infantile epileptic spasms scenario. In three out of six (50%) scenario's "off-label" use of ASM was reported. For the 2-year old girl with TSC, 11.6% would use "off-label" oxcarbazepine. The 6-month-old female infant with non-structural focal seizures would be treated by an "off-label" ASM by 38.4% of the respondents (i.e. oxcarbazepine, lamotrigine or carbamazepine). Regarding the 15-month-old girl with Dravet syndrome 8.3% and 24.1% would use "off-label" ASM, topiramate and stiripentol, as first- and second-line ASM respectively. There are known potential risks in prescribing "off-label" ASMs. Hence, pharmaceutical companies should include infants and young children in new clinical trials. Improvement of the design of clinical trials and methods promoting small groups would be helpful for both rare epilepsies and trials in infants.

AUTHOR CONTRIBUTIONS

JS: Formal analysis, Data curation, Writing (Original draft, review & editing), Visualization. LL, SA: Conceptualization, Methodology, Investigation, Writing (Review & editing), Formal analysis, Data curation, Supervision. All authors: Conceptualization, Methodology, Investigation, Writing (Review & editing).

CONFLICT OF INTEREST

JS has no conflict of interest to disclose. SA received honoraria or consultancy fees from Arvelle, Biomarin, Eisai, GW Pharma, Neuraxpharm, Nutricia, UCB Pharma, Xenon, Zogenix. SA is an associate editor for Epilepsia. AA, in agreement with his Institution, has served as principal investigator or member of DMCs. in clinical trials for Eisai, UCB, GW Pharma; received consulting fees from Jazz, Zogenix, Eisai, Takeda, Biocodex, Encoded Therapeutics and Neuraxpharm; unrestricted research grants from, UCB, Caixa Foundation and Jazz and academic research grants from EJP-RD and the EU. AA is Editor-in-Chief Emeritus for Epileptic Disorders (JLE editions) and Associate Editor for the European Journal of Pediatric Neurology (Elsevier). HC has acted as an investigator for studies with GW Pharma, Zogenix, Vitaflo, Stoke. Therapeutics and Marinus. She has been a speaker

and on advisory boards for GW Pharma, Zogenix, UCB and Nutricia; all remuneration has been paid to her department. She holds as endowed chair at UCL Great Ormond Street Institute of Child Health; she holds grants from NIHR, EPSRC, GOSH Charity, ERUK, the Waterloo Foundation and the National Institute of Health Research (NIHR) Biomedical Research Centre at Great Ormond Street Hospital. HH has no interests to declare. RP is an investigator for studies with UCB and does consultancy work for Kephala, Ireland. She served as a speaker and/or on Advisory Boards for Natus, GW, Eisai, and UCB. Her research is supported by the National Institute of Health Research (NIHR) Biomedical Research Centre at Great Ormond Street Hospital, Cambridge Biomedical Research Centre, the NIHR and the Evelyn Trust. KR has received honoraria for educational symposia, advisory boards and/or consultancy work from Eisai, LivaNova, Medlink Neurology, Novartis and UCB Australia Ltd. Her institution has supported clinical trials for Biogen Idec Research Ltd., DSLP, Eisai Inc., Epigenyx Therapeutics Inc., GW Research Ltd, Janssen-Cilag, Marinus Pharmaceuticals Inc., Medicure International Inc., LivaNova, Neurocrine Biosciences Inc., Noema Pharma, Novartis, SK Lifesciences Inc., UCB Australia Ltd., UCB Biopharma SRL and Zogenix Inc. KS received honoraria from Eisai. JW is a member of the South African Sanofi advisory board and is an associate editor for Epilepsia. EY has no conflict of interest to disclose. LL received grants, and is a consultant and/or speaker for Zogenix; LivaNova, UCB, Shire, Eisai, Novartis, Takeda/Ovid, NEL, Epihunter. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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REFERENCES

1. Kuchenbuch M, Chemaly N, Henniene KM, Kaminska A, Chiron C, Nabbout R. Off-label use and manipulations of antiepileptic drugs in children: analysis of the outpatient prescriptions in a tertiary center. Epilepsy Behav. 2018;82:133–9.
2. Löscher W, Klitgaard H, Twyman RE, Schmidt D. New avenues for anti-epileptic drug discovery and development. Nat Rev Drug Discov. 2013;12(10):757–76.
3. Perucca E, Brodie MJ, Kwan P, Tomson T. 30 years of second-generation antiseizure medications: impact and future perspectives. Lancet Neurol. 2020;19(6):544–56.
4. Seker Yilmaz B, Okuyaz C, Komur M. Predictors of intractable childhood epilepsy. Pediatr Neurol. 2013;48(1):52–5.
5. Striano P, Vari MS, Mazzocchetti C, Verrotti A, Zara F. Management of genetic epilepsies: from empirical treatment to precision medicine. Pharmacol Res. 2016;107:426–9.
6. Chiron C, Kassai B, Dulac O, Pons G, Nabbout R. A revisited strategy for antiepileptic drug development in children: designing an initial exploratory step. CNS Drugs. 2013;27(3):185–95.
7. Schmidt D. Efficacy of new antiepileptic drugs. Epilepsy Curr. 2011;11(1):9–11.
8. Rusz C-M, Ősz B-E, Jîtcă G, Miklos A, Bătrînu MG, Imre S. Off-label medication: from a simple concept to complex practical aspects. Int J Environ Res Public Health. 2021;18(19):10447.
9. Turner S, Nunn AJ, Fielding K, Choonara I. Adverse drug reactions to unlicensed and off-label drugs on paediatric wards: a prospective study. Acta Paediatr. 1999;88(9):965–8.
10. Bellis JR, Kirkham JJ, Nunn AJ, Pirmohamed M. Adverse drug reactions and off-label and unlicensed medicines in children: a prospective cohort study of unplanned admissions to a paediatric hospital. Br J Clin Pharmacol. 2014;77(3):545–53.
11. Anderson M, Egunsola O, Cherrill J, Millward C, Fakis A, Choonara I. A prospective study of adverse drug reactions to antiepileptic drugs in children. BMJ Open. 2015;5(6):e008298.
12. Bellis JR, Kirkham JJ, Thiesen S, Conroy EJ, Bracken LE, Mannix HL, et al. Adverse drug reactions and off-label and unlicensed medicines in children: a nested case-control study of inpatients in a pediatric hospital. BMC Med. 2013;11:238.
13. Schrier L, Hadjipanayis A, Stiris T, Ross-Russell RI, Valiulis A, Turner MA, et al. Off-label use of medicines in neonates, infants, children, and adolescents: a joint policy statement by the European academy of Paediatrics and the European society for developmental perinatal and pediatric pharmacology. Eur J Pediatr. 2020;179(5):839–47.
14. Chen Z, Li S, Zeng L, Liu Y, Zhang M, Choonara I, et al. Accessibility of medicines for children: a systematic review. Front Pharmacol. 2021;12:691606.
15. Wittich CM, Burkle CM, Lanier WL. Ten common questions (and their answers) about off-label drug use. Mayo Clin Proc. 2012;87(10):982–90.
16. Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Allen Hauser W, Mathern G, et al. Definition of drug resistant epilepsy: consensus proposal by the ad hoc task force of the ILAE commission on therapeutic strategies. Epilepsia. 2010;51(6):1069–77.
17. Rao VR, Lowenstein DH. Epilepsy. Curr Biol. 2015;25(17):R742–6.
18. Abend NS, Gutierrez-Colina AM, Monk HM, Dlugos DJ, Clancy RR. Levetiracetam for treatment of neonatal seizures. J Child Neurol. 2011;26(4):465–70.
19. Han JY, Moon CJ, Youn YA, Sung IK, Lee IG. Efficacy of levetiracetam for neonatal seizures in preterm infants. BMC Pediatr. 2018;18(1):131.

20. Falsaperla R, Scalia B, Giugno A, Pavone P, Motta M, Caccamo M, et al. Treating the symptom or treating the disease in neonatal seizures: a systematic review of the literature. Ital J Pediatr. 2021;47(1):85.
21. Kim J-S, Kondratyev A, Tomita Y, Gale K. Neurodevelopmental impact of antiepileptic drugs and seizures in the immature brain. Epilepsia. 2007;48(Suppl 5):19–26.
22. Katsarou A-M, Galanopoulou AS, Moshé SL. Epileptogenesis in neonatal brain. Semin Fetal Neonatal Med. 2018;23(3):159–67.
23. Carrasco M, Stafstrom CE. How early can a seizure happen? Pathophysiological considerations of extremely premature infant brain development. Dev Neurosci. 2018;40(5–6):417–36.
24. Sharpe C, Reiner GE, Davis SL, Nespeca M, Gold JJ, Rasmussen M, et al. Levetiracetam versus phenobarbital for neonatal seizures: a randomized controlled trial. Pediatrics. 2020;145(6):e20193182.
25. Glass HC, Soul JS, Chang T, Wusthoff CJ, Chu CJ, Massey SL, et al. Safety of early discontinuation of antiseizure medication after acute symptomatic neonatal seizures. JAMA Neurol. 2021;78(7):817–25. https://doi.org/10.1001/jamaneurol.2021.1437
26. Jindal A, Angurana SK, Suthar R, Kumar P, Sundaram V. Effect of early withdrawal of phenobarbitone on the recurrence of neonatal seizures: an open-label randomized controlled trial. Epilepsy Behav. 2021;117:107875.
27. Nickels K. Neonatal seizures: providing care with evidence, not just experience. Epilepsy Curr. 2021;21(6):427–9.
28. Pressler RM, Cilio MR, Mizrahi EM, Moshé SL, Nunes ML, Plouin P, et al. The ILAE classification of seizures and the epilepsies: modification for seizures in the neonate. Position paper by the ILAE Task Force on Neonatal Seizures. Epilepsia. 2021;62(3):615–28.
29. WHO (World Health Organization). Guidelines on neonatal seizures [Internet]. 2011 [cited 2022 Oct 15]. p. 100. Available from https://apps.who.int/iris/bitstream/handle/10665/77756/9789241548304_eng.pdf;jsessionid=841327C90522972E2D29C5A76DF1E231?sequence=1
30. Samanta D. Recent advances in the diagnosis and treatment of neonatal seizures. Neuropediatrics. 2021;52(2):73–83.
31. Keene JC, Morgan LA, Abend NS, Bates SV, Bauer Huang SL, Chang T, et al. Treatment of neonatal seizures: comparison of treatment pathways from 11 neonatal intensive care units. Pediatr Neurol. 2022;128:67–74.
32. Leung AK, Hon KL, Leung TN. Febrile seizures: an overview. Drugs Context. 2018;7:212536.
33. Offringa M, Newton R, Nevitt SJ, Leung TN. Prophylactic drug management for febrile seizures in children. Cochrane Database Syst Rev. 2021;6(6):CD003031.
34. Natsume J, Hamano S-I, Iyoda K, Kanemura H, Kubota M, Mimaki M, et al. New guidelines for management of febrile seizures in Japan. Brain Dev. 2017;39(1):2–9.
35. Capovilla G, Mastrangelo M, Romeo A, Vigevano F. Recommendations for the management of "febrile seizures": ad hoc task force of LICE guidelines commission. Epilepsia. 2009;50(Suppl 1):2–6.
36. Curatolo P, Nabbout R, Lagae L, Aronica E, Ferreira JC, Feucht M, et al. Management of epilepsy associated with tuberous sclerosis complex: updated clinical recommendations. Eur J Paediatr Neurol. 2018;22(5):738–48.
37. Annear NMP, Appleton RE, Bassi Z, Bhatt R, Bolton PF, Crawford P, et al. Tuberous sclerosis complex (TSC): expert recommendations for provision of coordinated care. Front Neurol. 2019;10:1116.
38. Northrup H, Aronow ME, Bebin EM, Bissler J, Darling TN, de Vries PJ, et al. Updated international tuberous sclerosis complex diagnostic criteria and surveillance and management recommendations. Pediatr Neurol. 2021;123:50–66.
39. Levetiracetam for the treatment of focal epilepsy in children from 1 month of age (FDA) [Internet]. [cited 2022 Oct 15]. Available from https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021035s099,021505s038lbl.pdf
40. Levetiracetam for the treatment of focal epilepsy in children from 1 month of age (EMA) [Internet]. [cited 2022 Oct 15]. Available from https://www.ema.europa.eu/en/documents/product-information/keppra-epar-product-information_en.pdf
41. NICE (National Institute for Health and Clinical Excellence) Guidelines. Epilepsies in children, young people and adults. 2022 [cited 2022 Oct 15]. p. 139. Available from https://www.nice.org.uk/guidance/ng217/resources/epilepsies-in-children-young-people-and-adults-pdf-66143780239813
42. O'Callaghan FJK, Edwards SW, Alber FD, Cortina Borja M, Hancock E, Johnson AL, et al. Vigabatrin with hormonal treatment versus hormonal treatment alone (ICISS) for infantile spasms: 18-month outcomes of an open-label, randomised controlled trial. Lancet Child Adolesc Health. 2018;2(10):715–25.
43. Fusco L, Serino D, Santarone ME. Three different scenarios for epileptic spasms. Epilepsy Behav. 2020;113:107531.
44. Lux AL, Edwards SW, Hancock E, Johnson AL, Kennedy CR, Newton RW, et al. The United Kingdom infantile spasms study (UKISS) comparing hormone treatment with vigabatrin on developmental and epilepsy outcomes to age 14 months: a multicentre randomised trial. Lancet Neurol. 2005;4(11):712–7.
45. Wirrell EC, Laux L, Donner E, Jette N, Knupp K, Meskis MA, et al. Optimizing the diagnosis and Management of Dravet Syndrome: recommendations from a north American consensus panel. Pediatr Neurol. 2017;68:18–34.e3.
46. Lagae L. Dravet syndrome. Curr Opin Neurol. 2021;34(2):213–8.
47. Cross JH, Caraballo RH, Nabbout R, Vigevano F, Guerrini R, Lagae L. Dravet syndrome: treatment options and management of prolonged seizures. Epilepsia. 2019;60(Suppl 3):S39–48.
48. Topiramate (FDA) [Internet]. [cited 2022 Oct 15]. Available from https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/020844s041lbl.pdf
49. Topiramate (EMA) [Internet]. [cited 2022 Oct 15]. Available from https://www.ema.europa.eu/en/documents/referral/questions-answers-referral-topamax-associated-names-topiramate-tablets-capsules_en.pdf
50. Cardenal-Muñoz E, Auvin S, Villanueva V, Cross JH, Zuberi SM, Lagae L, et al. Guidance on Dravet syndrome from infant to adult care: road map for treatment planning in Europe. Epilepsia Open. 2022;7(1):11–26.
51. Wirrell EC, Hood V, Knupp KG, Meskis MA, Nabbout R, Scheffer IE, et al. International consensus on diagnosis and management of Dravet syndrome. Epilepsia. 2022;63(7):1761–77. https://doi.org/10.1111/epi.17274
52. Wu J, Zhang L, Zhou X, Wang J, Zheng X, Hu H, et al. Efficacy and safety of adjunctive antiseizure medications for dravet syndrome: a systematic review and network meta-analysis. Front Pharmacol. 2022;13:980937.

53. Chilcott E, Díaz JA, Bertram C, Berti M, Karda R. Genetic therapeutic advancements for Dravet syndrome. Epilepsy Behav. 2022;132:108741.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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