Official Journal of the European Paediatric Neurology Society

Original article

Role of observational studies in supporting extrapolation of efficacy data from adults to children with epilepsy — A systematic review of the literature using lacosamide as an example

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ARTICLE INFO

Article history:
Received 29 January 2019
Received in revised form
8 April 2019
Accepted 6 May 2019

Keywords:
Paediatric
Seizures
Focal
Generalised
Trials

ABSTRACT

Extrapolation of efficacy data from adults to children is accepted for focal epilepsy – the antiepileptic drug, lacosamide, has been approved for the treatment of children ≥4 years of age on this basis. Since many small-scale, open-label studies are reported in the literature before approval, a systematic review was conducted to ascertain whether results of these could be used to support extrapolation in epilepsy in the future. In the absence of randomised trials, a second analysis was conducted for reports on lacosamide use in adults with generalized epilepsies. Twenty-seven articles were included in the paediatric qualitative synthesis, and 14 in the adult. Paediatric studies were analysed separately based on seizure type: focal, generalised and mixed. In focal epilepsy, safety and seizure-related findings mirrored those observed in the adult Phase II/III trials, supporting the feasibility of data extrapolation. Few studies reported outcomes in children with epilepsies associated with generalised seizures, and those that included children with different seizure types, mostly did not provide results separately. Lacosamide treatment appeared beneficial for children and adults experiencing tonic-clonic and myoclonic seizures. Reports of seizure aggravation were inconsistent and, in many cases, could not be clearly attributed to lacosamide. Given the absence of sufficient data, evidence for the feasibility of extrapolation was not as clear-cut as it was in focal epilepsy. These results highlight the complexities of conducting

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https://doi.org/10.1016/j.ejpn.2019.05.002

trials in the generalised epilepsy setting, and the importance of studies in the real-life setting and of analysing efficacy data per generalized seizure type and syndrome.

1. Introduction

Complex ethical and methodological challenges mean that few randomized controlled trials (RCTs) are conducted in the paediatric population, and off-label drug prescription is common.[1–3] This recognition by regulatory authorities has led to acceptance of extrapolation of efficacy data from adults to children if disease progression and response to treatment are similar in both groups, and provided that safety and pharmacokinetics are evaluated in prospective trials.[2,3] In epilepsy, however, differences in syndromes, aetiology and natural history between adults and children add further layers of complexity to analyses.[4,5] According to the Pediatric Epilepsy Academic Consortium for Extrapolation (PEACE), if antiepileptic drugs (AEDs) have been shown to be effective in adults with focal epilepsy, they can be considered effective in children ≥2 years of age with focal epilepsy.[4]

During development, the evidence base for a candidate AED is typically built in the adult focal epilepsy setting; building the evidence base in primary generalized epilepsy (PGE; or idiopathic or generalized genetic epilepsy) however, is more complex and challenging.[6] PGE is best viewed as a spectrum of epilepsies, or a group of specific syndromes, where patients can present with a predominantly single, or a combination of seizure types, namely typical absence, myoclonic and generalized tonic–clonic (GTC) seizures.[7] These epilepsies are less common than focal epilepsies, and myoclonic and absence seizures are difficult to quantify, even though they can occur with very high frequencies in some patients.[8,9] Another challenge explaining the paucity of RCTs in adults with PGE, is the typically low frequency of GTC seizures (GTCs), particularly when patients are treated by available AEDs. Since these syndromes are on a continuum,[10,11] it is unlikely that patients with typical absences, GTC or myoclonic seizures that occur in the context of juvenile absence epilepsy (JAE), juvenile myoclonic epilepsy (JME) or GTCs only, will respond differently to a given AED. Other epilepsies, corresponding to more severe forms of genetic and/or structural neurodevelopmental epileptic encephalopathies, for example Lennox-Gastaut syndrome (LGS) or Dravet syndrome, also present with generalized seizures such as tonic-clonic, myoclonic, tonic and drop-attacks, and therefore, with further challenges.

The AED, lacosamide (LCM), has been granted approval for the treatment of children ≥4 years of age with focal seizures based on data extrapolation. It exerts its therapeutic activity by binding to and enhancing slow inactivation of voltage-gated Na^+ channels; unlike traditional Na^+ channel-blocking AEDs such as carbamazepine or phenytoin, it has little effect on fast inactivation.[12] A Phase III RCT with patients aged ≥4 to <17 years with focal epilepsy has been completed.[13]

Since many small-scale, open-label studies are reported in the literature before approval, a qualitative analysis of the reports was conducted to ascertain whether evidence from such studies could be used to support data extrapolation in epilepsy in the future, using LCM as an example. Given that RCTs with LCM in adults with generalized epilepsies have not been completed, a qualitative analysis of reports in the literature was also conducted to allow comparison between adult and paediatric populations.

2. Methods

Analyses were designed and reported in accordance with PRISMA guidelines.[14,15]

2.1. Search strategy and screening

The first search was conducted in PubMed, EMBASE, BIOSIS, Derwent Drug File and Ovid MEDLINE using the following search terms in the title or in the summary/abstract of the document: lacosamide and pediatr*/paediatr* or child* or infant. The age range considered was 0–21 years to allow inclusion of several studies with relatively large patient numbers. While paediatric patients are typically defined as those up to the age of 18 years, the National Institute of Child Health and Human Development in the US includes the 19–21-year age group as late adolescence.[16] The second search was conducted in the same databases using the following search terms in the title of the documents: lacosamide and generalized or tonic-clonic, myoclonic, absence, genetic, idiopathic. No limits were applied to either search.

Reports were initially screened based on titles and abstracts only – these were evaluated independently by two reviewers, and discrepancies resolved by discussion. Potentially eligible reports were reviewed in full.

2.2. Data extraction

The following were extracted: study design (prospective, retrospective, case report), sample size, patients' age and seizure type/syndrome, treatment regimen (monotherapy or adjunctive), LCM dose, lifetime and concomitant AEDs and duration of treatment/follow-up. Outcomes of interest were seizure- and safety-related outcomes. Seizure outcomes, where available, included responder rates, seizure frequency, and seizure freedom. Seizure aggravation/exacerbation also was evaluated Safety outcomes included, where available, all

adverse event (AE) data – incidence and type of AEs, serious AEs, and discontinuation due to AEs.

2.3. *Data quality assessment*

Data quality was not assessed formally since there were no RCTs.

3. Results

3.1. *Overview*

In the first search, at the cut-off date of March 2018, 130 reports were identified and screened based on title/abstract (Fig. 1). Of these, 80 were congress abstracts; while screened initially, the decision was taken subsequently to exclude them given heterogeneity in reporting and incomplete information. Many of the abstracts were submitted several times to different congresses, and 18 were subsequently published as full articles included in the analysis. In the next step, 50 articles were reviewed in full for eligibility (Fig. 1). Review articles were excluded (n = 7), as were articles based on studies conducted in emergency settings, where LCM was administered intravenously for treating children with acute seizure exacerbation or status epilepticus (SE; n = 6). Other reasons for exclusion are listed in Fig. 1. In total, 27 articles were included in the qualitative synthesis; 23 were identified in the search, and a further four from references in the articles reviewed.

In the second search (generalized seizures in adults), 47 reports were identified and screened based on title/abstract. Given the small number of both full publications (n = 10) eligible for inclusion, and abstracts (n = 4), the latter were also included in the analysis. Reasons for excluding the remaining 33 reports are listed in Fig. 1.

3.2. *Studies in focal epilepsy*

Seven studies included children with focal epilepsy only (Table 1). Of note were two prospective studies, one that included 24 very young children (2–4 years of age), and another with 79 children, the largest of all the focal epilepsy studies.[17,18] The retrospective studies had smaller sample sizes (n = 12–22), and the mean age and age range of the children were relatively similar. Details of previous AEDs, concomitant AEDs, and initiation and maintenance doses used in the studies are provided in Supplementary tables.

3.2.1. *Seizure outcomes*

In the three prospective studies, ≥50% responder rate was relatively similar (42%, 40.6% and 36%); however, there was divergence in the seizure freedom rate, with 44.3% reported by Pasha et al., and 17% and 14% in the other two studies.[17–19] In the four retrospective studies, outcomes were provided at varying time points; at 3 and 6 months, and at last follow-up with medians of 4 and 10 months. Across these retrospective studies, ≥50% responder rate ranged from 37.5% to 67%.[20–23] Seizure-freedom was similar in three studies (16.6%, 18.7% and 19%), while in the fourth,[21] only one child achieved seizure-freedom, but 23% experienced >90% seizure reduction.

Finally, Liguori et al. reported the case of a child with nocturnal frontal lobe epilepsy, who despite treatment with oxcarbazepine and clonazepam, was still experiencing nocturnal seizures.[24] Introduction of LCM resulted in abrupt seizure reduction, and following discontinuation of other

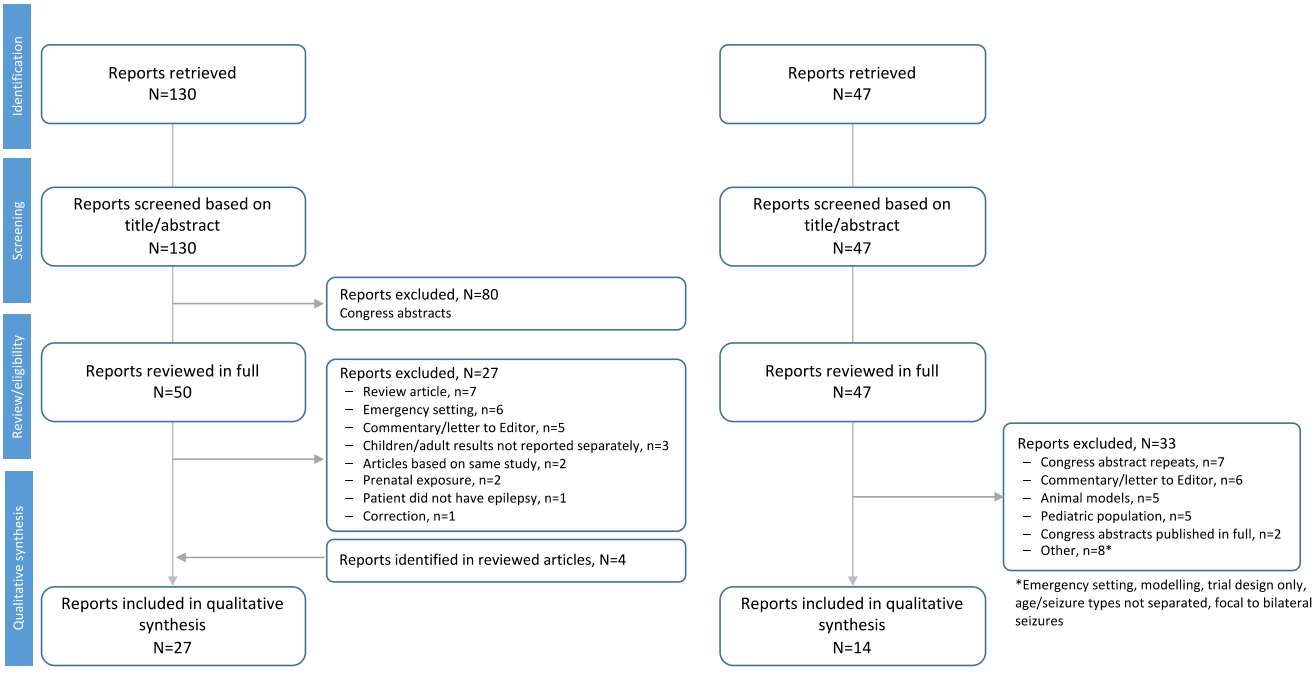

Fig. 1 – Flow of information in the systematic reviews. Results for the paediatric literature search are shown in the left panel, and for the adult literature search in the right panel.

Table 1 – Paediatric studies in focal (partial-onset) epilepsy.

Study	N	Age[a] (years)	Follow-up (months)	Seizure outcomes (change in frequency)	Safety outcomes (Incidence, AEs, discontinuation due to AEs)	Aggravation[b]
Prospective						
Grosso 2014[17]	24	Mean 2.7 (2–4)	Mean 10.3 (3–26)	At 3 months – ≥50% reduction 42% – 100% reduction 17%	– Incidence 33% – Drowsiness (21%), nervousness (12.5%), vomiting (8%), instability/difficulty walking (4%) – Discontinuation 4% (n = 1) due to walking instability	4% (n = 1)
Pasha 2014[18]	79	Mean 8.8 (5–15)	Mean 3	At 3 months – ≥50% reduction 40.6% – 100% reduction 44.3%	– Incidence 50.6% – Hyperactivity, ataxia, drowsiness, insomnia, weight gain, nausea, abdominal discomfort, giddiness, headache, vomiting – Discontinuation 2.5% (n = 2), due to aggressive behaviour, severe vomiting (1 each)	5.1% (n = 4)
Gavatha 2011[19]	14	Mean 10 (3–18)	Mean 8 (3 weeks –17 months)	Mean 5 months (3–8) – ≥50% reduction 36% – 100% reduction 14%	– Incidence 39% – Somnolence (16.7%), irritability (11.1%), sleep disturbances, pancytopenia (both 5.6%) – Discontinuation 5.6% (n = 1) due to pancytopenia	Not reported
Retrospective						
Yildiz 2017[20]	12	Mean 13.8 (6.2 –17.6)	Mean 23 (11–37)	At 6 months – ≥50% reduction 58.0% – 100% reduction 16.6%	– Incidence not given – Common AEs – dizziness, ataxia, nausea and vomiting – Discontinuation 16.6% (n = 2) due to status epilepticus	Not reported
Toupin 2015[21]	22	Mean 12.9 (5.2 –20.7)	Mean 11.9 (3–35)	At 3 months – ≥50% reduction 59% – 90% reduction 23%	– Incidence 50% – Drowsiness, dizziness (both 23%), incoordination (14%), irritability, insomnia (both 9%), headache, blurred vision, nausea (each 5%) – Discontinuation 13.6% (n = 3) due to mild but persistent AEs	Not reported
Kim 2014[22]	21	Median 13.9 (1.2 –17.9)	Median 10.1 (6.1 –13.0)	At last follow-up – ≥50% reduction 67% – 100% reduction 19%	– Incidence 38% – Somnolence (14.3%), dizziness, personality change (both 9.5%), sleep disturbance, nausea (both 4.8%) – Discontinuation 10% (n = 2) due to aggressive behaviour and depression (1 each)	Not observed

Table 1 – (continued)

Study	N	Age[a] (years)	Follow-up (months)	Seizure outcomes (change in frequency)	Safety outcomes (Incidence, AEs, discontinuation due to AEs)	Aggravation[b]
Guilhoto 2011[23]	16	Mean 14.9 (8–21)	Median 4 (1–13)	At last follow-up – ≥50% reduction 37.5% – 100% reduction 18.7%	– Incidence 12.5% – Worsening chronic headache, nausea and blurred vision (both 6.25%, n = 1) – Discontinuation 25% (n = 4) due to oral tics, severe behavioural outbursts, seizure worsening with vomiting, and ataxia and depression associated with suicidal ideation (1 each)	6.2% (n = 1)

[a] At study entry.
[b] All cases of aggravation involved an increase in seizure frequency.

AEDs, the patient remained seizure-free at the 12-month follow-up on LCM monotherapy.

There were no reports of seizure aggravation in three studies.[19,21,22] In the largest study, four patients (5.1%) experienced an increase in seizure frequency; however, none discontinued.[18] A patient each in two of the smaller studies also reported an increase, with one discontinuing due to the increase.[17,23] In another of the smaller studies, there were no reports of aggravation, but two patients developed SE.[20]

3.2.2. *Safety outcomes*

In the largest study, the prospective study by Pasha et al., AEs were reported by 50.6% of patients, mostly mild-to-moderate in intensity, and only two patients discontinued due to AEs; one due to severe vomiting and the other due to aggressive behaviour.[18] Further details on the latter was published in a safety case report.[25] The authors also assessed behaviour using the Conners Comprehensive Behaviour Rating Scale.[26] The score was 48.04 ± 10.57 at baseline and 19.27 ± 8.03 after 3 months' treatment with LCM, representing a statistically significant improvement in behaviour. The significant reduction in seizure frequency during the study may have contributed to the improvement in behaviour.

In the study with very young children, incidence of AEs was 33%.[17] These were described as being tolerable and transient, and only one patient discontinued (due to walking instability). In the third prospective study, incidence of AEs was 39% and one patient discontinued due to AEs (pancytopaenia).[19]

Incidence of AEs ranged from 12.5% to 50% and discontinuation from 10% to 25% in three retrospective studies.[21–23] The incidence was not given in one of the studies; as noted above, two patients developed SE, one on day 3 and the other on day 11 of treatment with LCM, and both discontinued treatment.[20] Most commonly reported AEs across all studies were drowsiness, dizziness, nausea, vomiting, ataxia (also reported as instability or incoordination), and sleep disturbances.

3.3. *Studies with mixed populations*

Nine studies included children with focal or generalized epilepsies (Table 2). Overall, the studies varied largely in sample size and patient population. Four studies in particular had large sample sizes; one conducted in the US with 223 patients,[27] and three in Spain with 191, 130 and 88 patients.[28–30]

3.3.1. *Seizure outcomes*

Seizure (and safety) outcomes were not reported consistently in the retrospective studies; three reported outcomes at 3 months and the remainder at the last follow-up. The ≥50% responder rate at 3 months in the two large prospective studies was 47.4% and 62.3%, and seizure-freedom 6.8% and 13.8%.[29,31] In the smaller study, ≥50% responder rate was 50% at last follow-up and no patients were seizure-free.[32] A mix of seizure outcomes and retention rate was provided with wide variation. For example, 1-year retention was 45% and 72.8% in the two largest studies, by McGinnis and Kessler, and Sanmarti et al., respectively.[27,28]

Heyman et al. and Gulati et al. did not provide a breakdown of results according to seizure type.[33,34] In three studies, patients with focal seizures appeared to respond better to LCM than patients with generalized, or mixed seizures. Rastogi and Ng reported that 2 of 8 (25%) patients with generalized epilepsy showed >90% seizure reduction, both of whom had LGS, while 5 of 8 (62.5%) patients with focal epilepsy had ≥50% reduction in seizures.[32] In the study by Verrotti et al., ≥50% responder rate at 3 months was 33.3%, 36.8%, 71.4% and 57.1% among patients with generalized (n = 12), focal (n = 19), focal evolving to bilateral (secondary generalization) (n = 7), and mixed (n = 21) seizures, respectively.[31] Only patients with focal or generalized seizures achieved seizure-freedom, 8.3% and 15.8%, respectively. Sanmarti et al. did not provide separate results, but in their analysis of factors contributing to treatment response, they reported that there was a trend

Table 2 – Paediatric studies with mixed populations – focal (partial-onset) and generalised seizures, including focal to bilateral (secondary generalisation).

Study	N	Age[a] (years)	Seizure type (%)	Follow-up (months)	Seizure outcomes (change in frequency)	Safety outcomes (Incidence, common AEs, discontinuation due to AEs)	Aggravation[b]
Prospective							
Verrotti 2013[31]	59	Mean 11 (4–15)	– Focal 32.2 – Generalized 20.3 – Focal to bilateral 11.9 – Mixed 35.6	Mean 11[c] (3–15)	At 3 months – ≥50% reduction 47.4% – 100% reduction 6.8%	– Incidence 30.5% – Dyspepsia (6.8%), headache, vomiting, nausea, irritability (5.1% each) – Discontinuation 3.4% (n = 2) both due to vomiting	11.9% (n = 7)
Casas-Fernández 2012[29]	130	Mean 8 (0.5–16)	Breakdown not given	3	At 3 months – ≥50% reduction 62.3% – 100% reduction 13.8%	– Incidence 30% – Nausea/vomiting (10%), instability (7.7%), dizziness (3.8%) – Discontinuation 10% (n = 13), one due to SE	3.8% (n = 5)
Rastogi 2012[32]	16	Mean 9 (1–16)	– Focal 50 – Generalized 50	Mean 10 (3–18)	At last follow-up – ≥50% reduction 50%	– Incidence not reported – Nausea, vomiting, gastrointestinal intolerance, dizziness, headache, somnolence, facial oedema, and increased seizures	Not reported
Retrospective							
Rosati 2018[30]	88	Median 10.5 (4m–18y)	– Focal 61.8 – Generalized 23.5 – Both 14.7	Median 10 (0–76)	6-month RR 74.4% 12-month RR 47.7%	– Incidence 12.5% – Dermatological (4.5%) and behavioural (3.4%) – Discontinuation 11.3%	Not reported
Sanmarti -Vilaplana 2018[28]	191	Mean 9.4	– Focal 65.4 – Generalized 33.5 – Both 1.0	Minimum 12	At 3 months – ≥50% reduction 37.3% – 100% reduction 9.7% 12-month RR 72.8%	– Incidence 28.8% – Diplopia (5.2%), dizziness (3.7%), ataxia and drowsiness (each 2.1%) – Discontinuation 2% AEs only, 2% combination of AEs and lack of efficacy, 10% seizure	14.7% (n = 28)
McGinnis 2016[27]	223	Median 13 (1.4–20.9)	– Focal 75 – Generalized 5 – Both 19	Median 7.4 (1–53)	12-month RR 45%	– Incidence 42% – Drowsiness (16%), behavioural/mood disturbance (11%), dizziness (10%), GI upset/nausea (8%), motor symptoms/ataxia (5%) – Discontinuation 10% AEs; 12% combination of AEs/lack of efficacy	Not reported
Gulati 2015[34]	40	Median 11 (2–19)	– Focal 90 – Generalized 10	Median 10.5 (1–29)	At 3 months – ≥50% reduction 20% – 100% reduction 5% 9-month RR 65%	– Incidence 17.5% – Drowsiness, mood change (both 10%) – Discontinuation 0	10% (n = 4)[d]

Yorns 2014[35]	40	Mean 12.3 (1.4–20.8)	– Focal 42.5 – Generalized 57.5	Mean 9.2 (1.7–28.3)	At last follow-up – ≥50% reduction 42.5% – 100% reduction 15%	– Incidence 37.5% – Lethargy, worsening behaviour (both 10%), weight loss, dizziness (both 5%) – Discontinuation 5% (n = 2), due to head tremor and worsening behaviour (n = 1 each)	7.5% (n = 3)
Heyman 2012[33]	17	Mean 8 (1.5–16)	– Focal 53 – Focal to bilateral 17 – Mixed 29	Mean 9.1 (1–18)	At last follow-up – ≥50% reduction 35%	– Incidence 59% – Nausea, dizziness (both 18%), restlessness, fatigue, headache (12% each), increased appetite, prolonged crying (both 6%) –Discontinuation 0	11.7% (n = 2)

RR = retention rate.
[a] Age at study entry.
[b] All cases of aggravation involved an increase in seizure frequency, except for the Yorns et al. study, where 2 patients reported longer seizures than usual but with the same frequency.
[c] Study duration is for overall population, which includes patients in the older age group.
[d] All cases reported before start of evaluation period, and were excluded from the study.

toward focal epilepsy being associated with treatment response (odds ratio 1.83; 95%CI 0.94–3.56; p = 0.074).[28]

In the remaining four studies, treatment response did not differ according to seizure type. Casas-Fernandez et al. noted the absence of any relationship between response and epileptic syndrome, and that two of two patients with LGS reported >50% seizure reduction.[29] In the study by Yorns et al., more children with generalized epilepsy showed improvement than those with focal epilepsy; however, the difference was not statistically significant (57.5% vs 42.5%).[35] Rosati et al. did not observe significant differences in response based on epilepsy and seizure types – 12-month retention rate was 47.7% for all patients, and 41.8%, 69.2% and 50.0% for children with focal, generalized, and combined epilepsy, respectively.[30] They also analysed median time-to-relapse for responders with focal, generalized, or combined epilepsy, which was 45, 49, and 37 months, respectively. No significant differences were observed with regard to epilepsy and seizure type. Similarly, McGinnis and Kessler, who conducted the study with the largest population, did not find a significant difference in retention among patients with focal seizures only (n = 168) compared with those who had seizures with generalized onset or both generalized and focal seizures (n = 55; hazard ratio 0.94, 95% CI 0.66–1.35, p = 0.75).[27] Again, retention rate did not differ among patients with focal discharges on EEG or those with multifocal or generalized discharges (HR 0.97, 95% CI 0.70–1.36, p = 0.87).

There were no reports of seizure aggravation in three studies.[27,30,32] In their large-scale prospective study, Casas-Fernandez et al. reported an increase in seizure frequency in five (3.8%) patients; all had focal seizures (three with focal to bilateral seizures), but none discontinued.[29] In another prospective study, Verrotti et al. reported an increase in seven (11.9%) patients, all of whom discontinued; four patients had generalised, two mixed, and one focal seizures.[31] Sanmarti et al. reported an increase in 28 (14.7%) patients, with 19 (10%) discontinuing.[28] In the study by Gulati et al., four children (10%) experienced an increase before the 3-month evaluation period and were excluded from the safety and efficacy analyses.[34] Finally, Yorns et al. reported seizure aggravation in three children (7.5%), one experienced increased frequency, while the other two experienced longer seizures than usual; none discontinued treatment.[35]

3.3.2. *Safety outcomes*

Incidence of AEs was similar in the two larger prospective studies, 30% and 30.5%; discontinuations were 10% and 3.4%.[29,31] In the third smaller study, incidence of AEs was not provided.[32] The authors stated that LCM was well tolerated, even at high doses (up to 19.4 mg/kg/day), and AEs were similar to those described in adults, with the exception of facial oedema, reported in one child. There were no discontinuations.

In the retrospective studies, incidence of AEs ranged from 12.5% to 59%. The highest incidence (59%) was seen in a small study with 17 patients; however, none discontinued due to AEs.[33] Discontinuations in the other studies ranged from 0 to 11.3%. The most frequently reported AEs in all these studies, prospective and retrospective, were nausea, vomiting, dizziness, somnolence/lethargy, irritability (or instability, restlessness), and behavioural disturbances.

3.4. *Epilepsies with predominantly generalized seizures and epilepsy syndromes – paediatric population*

Three studies and four case reports were identified. One study included 21 children with generalized epilepsies only.[36] At 3 months, ≥50% reduction in seizure frequency was 43% and seizure freedom 24%. None of the eight children with LGS became seizure-free; however, seven (87.5%) experienced ≥50% reduction in seizure frequency. Among the children with other types of generalized epilepsy, five (38.5%) became seizure-free, 15.4% showed ≥50% improvement, while 38.5% showed no change. Seizure aggravation was not reported. Adverse events were reported in 6 patients (28.6%) and one discontinued due to AEs.

Grosso et al. included 18 children with LGS in one study.[37] After a median follow-up of 9 months, ≥50% reduction in seizure frequency was 33%, and overall reduction 29%; the highest response was with tonic seizures (31%) and the lowest with drop-attacks (20%). None of the patients became seizure-free. The incidence of AEs was 44%, with dizziness, nausea, vomiting reported most frequently. Four children discontinued treatment; three due to increased tonic seizures and drop-attacks and one due to walking instability. In a critique of this study, Andrade-Machado et al. observed that four patients did not have tonic seizures, and therefore, could not have had LGS.[38] A report described the case of a 20-year female diagnosed with LGS and cryptogenic hepatopathy, who had failed to respond to seven AEDs.[39] LCM was administered intravenously – it resulted in worsening of tonic seizures and EEG pattern, and was discontinued. Among the studies with mixed populations described in section 3.3, several provided separate results for patients with LGS – these are summarized in Table 3.

Afra and Adamolekun described the cases of two patients with JME; one had been seizure-free on LCM monotherapy for 12 months, and the other for 18 months on LCM and valproate combination therapy.[40] No AEs were reported, and the authors noted that there was no seizure exacerbation. Another case report was of a 21-year-old with JME who experienced seizure freedom for 18 months at last follow-up with LCM and zonisamide combination therapy.[41] No AEs were reported. In their study population of 40 children, Yorns et al. included two with JME, but only provided results for one patient separately.[35] This patient was experiencing several GTC seizures per day at study start, but was reported to be seizure-free for over a year after LCM initiation.

Grosso et al. reported findings from eight patients displaying CSWS who underwent neuropsychological investigations before, and 6 months after treatment with LCM.[42] At this point, seven patients showed better attention at school, were more alert and less anxious; an improvement considered significant by parents and teachers. Analysis of 24-h EEGs showed that six (75%) patients were ≥50% responders with 24-h EEG normalization in three of them, one patient showed a 40% reduction, and another failed to respond to LCM. The investigators reported that LCM was well tolerated by all patients.

3.5. *Safety case reports*

Four case reports were identified describing safety observations only. Details are provided in Supplementary material.

3.6. *Epilepsy syndromes with predominantly generalized seizures – adult population*

Of 14 reports identified, only one was of a prospective trial; the remainder were either small-scale retrospective studies or case reports/series (Table 4). The prospective trial was a 13-week Phase II, open-label trial, which included 49 patients with uncontrolled PGE; 39 patients subsequently entered a 59-week, flexible-dosing extension.[43] Results showed that treatment with adjunctive LCM was associated with a reduction in the number of seizure days throughout the trial and its extension. Seven patients reported an increase in seizure frequency; five absence, one myoclonic and one GTC. Four of these patients discontinued due to this increase. The incidence and nature of other AEs were similar to those reported in the focal epilepsy trials.

Three retrospective studies, and a case report, also included patients with PGE. In a study by Abarrategui et al., seven of nine patients showed ≥50% reduction in seizure frequency, with four (two with JME and two with absence seizures) remaining seizure-free for several years.[44] Of two non-responders, one had JAE and discontinued due to myoclonia and absence SE, while the other had GTCs only, and subsequently became seizure-free after addition of valproate. In the studies by Afra et al., and Arnold and Beige, with 10 patients each, most also responded to treatment with LCM.[45,46] In the former, two patients with atypical absence epilepsy did not respond to LCM, and one patient with JAE discontinued due to development of a rash.[45] There were no reports of seizure aggravation. One patient in the study by Arnold and Beige experienced an intermittent, self-limiting increase in myoclonic seizures and three discontinued treatment due to a combination of AEs and lack of efficacy.[46] Zangaladze et al. described the case of a patient with GTC and absence seizures who became seizure-free.[41]

Two JME case reports were identified; both patients experienced exacerbation of myoclonus.[47,48] However, in the aforementioned studies by Abarrategui et al. and Arnold et al., seven patients with JME benefited from treatment.[44,46] A patient with JME reported by Afra et al. experienced 4-month seizure-freedom with LCM, but discontinued due to fatigue, depression and anxiety.[45] Finally, Polovitz et al. reported the case of a patient with myoclonic epilepsy who experienced a reduction of hourly myoclonic events to approximately three weekly events.[49]

Two studies and two case reports included a total of 41 patients with LGS. Investigators in one study reported seizure reduction in some patients, but not aggravation[50]; in the second study, while aggravation of tonic and astatic seizures was reported, a strong suppressive effect on GTC and focal seizures was noted.[51] In a case series of three patients, all experienced tonic seizure aggravation and discontinued

Table 3 – Paediatric studies in epilepsy syndromes and epilepsies associated with generalized seizures.

Study	N	Syndrome	Age (years)	Follow-up (months)	Change in seizure frequency	Safety outcomes (AE incidence, discontinuation due to AEs)
Miskin 2016[36]	8 4 4 5	– LGS – JME – JAE – Other[a]	Mean 11.9 (4–19.5)	Mean 19 (3–43.2)	100% reduction, n = 5 (23.8%) ≥50% reduction, n = 9 (43%) No change, n = 7 (33.3%) Seizure aggravation not reported	– Incidence 28.6% – Somnolence (9.5%), weight loss, tremor, memory problems, nausea, dizziness (4.8% each) – Discontinuation 4.8% (n = 1)
Grosso 2014[37]	18	LGS	Mean 12.3 (5.6–15)	Mean 9 (3–17)	≥50% reduction, n = 6 (33%) <50% reduction, n = 1 (5.5%) No change, n = 8 (44%) Increase in tonic seizures/drop attacks, n = 3 (17%)	– Incidence 44% – Most common dizziness, vomiting, nausea – Discontinuation 22% (n = 4), due to increased seizure frequency (n = 3), walking instability (n = 1)
Grosso 2014[42]	8	CSWS	Mean 9.8 (8.2–15.9)	6	≥50% reduction in spike wave index, n = 6 (75%) >40% reduction in spike wave index, n = 1 (12.5%) No response, n = 1 (12.5%)	Not reported
Afra 2012[40]	2	JME	Both 19	12 18	Seizure freedom at last follow up, n = 2 Seizure aggravation not observed	Not reported
Zangaladze 2012[41]	1	JME	21	18	Seizure freedom at last follow up Seizure aggravation not reported	Not reported
Andrade-Machado 2012[39]	1	LGS	20	2 days	Worsening of tonic seizures and EEG pattern	Not reported
Studies with mixed populations providing seizure outcomes separately for children with epilepsy syndromes[b]						
Rastogi 2012[32]	4	LGS			≥90% reduction, n = 2 No change, n = 2	
Casas-Fernández 2012[29]	2	LGS			≥50% reduction, n = 2	
Heyman 2012[33]	2	LGS			Increase, n = 2	
Yorns 2014[35]	2	JME			Seizure freedom at last follow up, n = 1 Results not provided for second patient	

CSWS = continuous spike-waves during sleep; JAE = Juvenile absence epilepsy; JME = juvenile myoclonic epilepsy; LGS = Lennox-Gastaut syndrome; PGE = primary generalized epilepsy.

[a] Unclassified generalized epilepsies, n = 4 and Doose syndrome, n = 1.

[b] Age and safety outcomes not provided separately; full study details are provided in Table 2.

Table 4 – Adult studies with epilepsy syndromes associated with generalized seizures.

Study	N	Age (years)	Diagnosis	Maintenance dose	Duration	Outcomes
Wechsler 2017[43]	49	Mean 29.7 ± 10.1	PGE – All patients had a history of GTCs – 69% absence seizures – 55% myoclonic seizures	Main trial Mean 295.2 ± 57.7 mg/day	13 weeks	Phase II trial (NCT01118949) (N = 49) – Median reduction in seizure days – absence 30.2%; myoclonic 68.1%; GTC 100% – Most common AEs – dizziness (n = 19), nausea (n = 13), headache and somnolence (n = 8 each) – 5 patients reported increased absence seizures – 5 patients discontinued: petit mal epilepsy (n = 2), dizziness, grand mal convulsion, and a combination of AEs (n = 1 each)[b]
				Extension Mean modal 428.2 ± 135.6 mg/day[a]	59 weeks	Extension trial (NCT01118962) (N = 39) – Reduction in seizure days maintained – Most common AEs – dizziness (n = 10), URTI (n = 10), headache (n = 7) and tremor (n = 6) – 2 patients discontinued due to AEs – one due to abnormal behaviour, and another due to confusional state – Increased absence seizures (resolved with dose reduction) n = 1; self-limiting increased myoclonic seizures (resolved without dose reduction) n = 1
Abarrategui 2017[44]	9	33–63	– CAE persisting into adulthood, n = 2 – JAE, n = 2 – JME, n = 2 – GTCs, n = 3	Median 300 mg/day (200–400)	6 months	– At 6 months ≥ 50% reduction in seizure frequency, n = 7 (77.7%) – Two patients were non-responders – one with JAE discontinued due to myoclonia and absence SE, and another with GTCs only did not improve on LCM, but became seizure-free after addition of VPA – After a median follow-up of 155 weeks, 8 of 9 patients remained on LCM; there were no reports of seizure aggravation, or AEs after the first 6 months – Two patients with JME and two with absence and GTCs remained seizure-free at last follow-up (≥2 years)
Birnbaum 2017[47]	1	64	Likely JME	Not given	Not given	Exacerbation of myoclonus
Swaminathan 2015[48]	1	42	JME	Not given	Not given	Exacerbation of myoclonus
Zangaladze 2012[41]	1	22	GTCs and absence seizures	400 mg/day	6 months	Patient seizure-free at 6-month follow-up
Afra 2012[40]	1	23	JME	400 mg/day	4 months	Patient experienced 4-month seizure-freedom, but discontinued due to fatigue, depression and anxiety
Afra 2010[45]	10	19–52	– GTCs, n = 4 – JAE, n = 1 – JAE and GTCs, n = 3 – AAE, n = 2	Up to 700 mg/day	1.5–11 months	– GTCs, 2 patients became seizure-free, 2 showed marked reduction – JAE, patient became seizure-free, but discontinued due to development of rash – JAE and GTCs, one patient became seizure-free, one had no further GTCs and a reduction in absence seizures, one patient showed no response – AAE, neither patient showed response

Arnold 2010[46]	10	20–62	– JME, n = 5 – GTCs,[c] n = 2 – Absence epilepsy, n = 3	100–300 mg/day	>6 months	– 100% reduction in seizure frequency, n = 2; ≥75%, n = 3; ≥50%, n = 2 – No increase in GTCs or absence seizures; one patient experienced an intermittent, self-limiting increase in myoclonic seizures – Three patients discontinued treatment due to side effects (tiredness, n = 2) and lack of efficacy (n = 2)[d]
Polovitz 2010[49]	1	42	Progressive myoclonic epilepsy type 1	Not given	Not given	Reduction from hourly myoclonic events to approximately three events weekly and improvement in speech with less stuttering and pausing
Algahtani 2018[53]	1	22	LGS	400 mg/day	Not given	Treatment caused excessive non-ictal laughing, but was maintained given effective seizure control (laughter subsequently controlled with selective serotonin reuptake inhibitor and atypical antipsychotic)
Andrade-Machado 2015[51]	19	18–61	LGS	Median 200 mg/day (50–300)	Follow-up 18 months Number of treatment days 90 (25–540)	– ≥50% reduction in seizure frequency, n = 2 (10.5%); <50%, n = 1 (5.3%) – Increased seizure frequency – tonic n = 16 (78.9%); astatic n = 7 (36.8%); tonic-clonic n = 0 – Most commonly reported AEs – worsening of seizures, aggressiveness, and irritability (each 47.7%), and somnolence (31.6%)
Bermejo 2014[50]	18	18–27	LGS	Not given	Mean follow-up 6.6 ± 2.1 months	– ≥50% reduction in seizure frequency, n = 6 (33%); small reduction, n = 7 (38%) – Two (11%) patients discontinued due to lack of efficacy – Three (17%) patients reported AEs
Cuzzolo 2010[52]	3	27 38 25	LGS	200 mg/day 200 mg/day 100 mg/day	6 weeks 8 weeks 2.5 weeks	– Aggravation of tonic seizures, weight loss and nausea – Tonic status epilepticus – Aggravation of tonic seizures, somnolence, and vomiting

AAE = atypical absence epilepsy; CAE = childhood absence epilepsy; EEG = electroencephalographic; JAE = juvenile absence epilepsy; GTCs = generalized tonic clonic seizures; PGE = primary generalised epilepsy; SE = status epilepticus; URTI = upper respiratory tract infection.

[a] Modal dose is defined as the daily dose a patient received for the longest duration during the treatment period.

[b] Combination of vertigo type feelings, diplopia, unsteady gait, hallucinations, nausea, sedation, and blurry vision.

[c] Grand mal epilepsy in the abstract.

[d] As reported verbatim in the abstract.

treatment,[52] while in another report, a single patient experienced episodes of excessive laughter, but the patient and her family opted to continue treatment as she had achieved good seizure control.[53]

4. Discussion

The most relevant factor when considering the evidence for data extrapolation is seizure type, since it is the basis for AED indications and licensing.[3] The case with focal epilepsies is the most straightforward, as these present almost exclusively with focal seizures (with or without focal to bilateral seizures). Extensive, wide-ranging analyses have shown that the underlying pathophysiology of focal seizures, as well as the electrographic features, are similar in adults and children >2 years, with the exception of those associated with epileptic encephalopathies such as LGS.[3–5] Consequently, evidence for a similar response in both adults and children with focal seizures to specific AEDs is compelling. In this analysis, seven studies included children with focal epilepsy only – the 50% responder rate ranged from 36% in a prospective study,[19] to 67% in a retrospective study.[22] Seizure-freedom, at 45%, was highest in the prospective study by Pasha et al.[18] Overall, response rates in these studies were similar to, or higher than those obtained in the Phase II/III, RCTs of adjunctive LCM in adults with focal epilepsy.[54–56] In a paediatric RCT, the 50% responder rate was 52.9% (n = 170) for LCM- and 33.3% (n = 168) for placebo-treated children.[13]

Nine studies included children with focal or generalized seizures; 50% responder rate ranged from 62.3% in a prospective study[29] to 20% in a retrospective study.[34] Although responder rate in the latter was the lowest of all, retention rate at 9 months was 65%. Importantly, among the 40 children, 11 had failed resective surgery, nine ketogenic diet, and five VNS. Retention rate was the main outcome in two of the large studies; at 1-year, retention was 45% in the study by McGinnis and Kessler,[27] and 47.7% in the study by Rosati et al.[30] Results were not broken down according to specific generalized seizure type; however, some overall insight was provided in most studies. In three studies, children with focal seizures responded better than those with generalized seizures,[30–32] and vice versa in another.[35] In three studies, there was no difference in response to LCM based on seizure type, including the largest prospective[29] and retrospective studies,[27,30] with a combined population of 441 patients.

Seven reports provided outcomes for children with predominantly generalized seizures and epilepsy syndromes, including patients with PGEs (such as JME) and genetic/structural neurodevelopmental epileptic encephalopathies (such as LGS). Some studies with mixed populations also provided results separately for patients with LGS, which is one of the most severe epileptic encephalopathies with childhood onset, and consequently, one of the most challenging epilepsies to manage; none of the currently available medications are consistently effective.[57,58] As such, extrapolation of efficacy results in adults with LGS to children is not feasible. Nonetheless, given the importance of finding efficacious AEDs for these patients, results for LCM in both adults and children were evaluated. In both groups, results were relatively similar, in that while some patients experienced aggravation of tonic seizures, other derived benefit from LCM. As noted by Andrade-Machedo et al., who conducted a study with 19 adults, the decision to start LCM needs to be determined on a case-by-case basis in patients with LGS, after consideration of the benefit-risk balance.[51]

Patients with PGE experience a variety of seizures. Currently, there is no evidence to suggest different pathophysiology for each of the seizure types in relation to the epilepsy in which it is observed. Correspondingly, there are no data indicating whether a patient experiencing a GTC or myoclonic seizure would respond differently to a given AED if it was administered for the control of this type of seizure in the context of JME or GTCs only. Therefore, it is important to determine the responsiveness of a specific type of generalized seizure that occurs in different syndromes. In other words, are GTCs that occur in the context of PGE or LGS (independently of underlying aetiology) equally responsive to a given AED? Another complex challenge when treating patients with multiple seizure types is to ensure that when an AED is prescribed with the aim of controlling one seizure type, it will not have an aggravating effect on the others. Seizure aggravation – increase in seizure frequency or emergence of new seizure types – with AED treatment is a common and clinically important problem in both children and adults.[59] Reasons for aggravation remain unknown; however, some contributing factors include spontaneous fluctuations in seizure frequency, presence of known aggravators, epilepsy progression, and development of drug resistance.[59–61] In children, aggravation, which can be a non-specific manifestation of drug toxicity, is more likely to occur in those with severe, drug-resistant epilepsy, or epileptic encephalopathy, who are typically on polytherapy.[60,61]

In the paediatric setting, overall, there were few reports of patients with PGE only, most having been reported in the studies with mixed populations. A single study included 21 children with generalised epilepsies, including eight with LGS.[36] Seizure aggravation was not reported. In the study by Yorns et al., one patient with JME who had been experiencing several GTCs per day at study start, was seizure-free for over a year after LCM initiation.[35] Afra and Adamolekun described the cases of three patients with JME, two of whom were younger than 21 years, while the third was 23 years of age.[40] All three were experiencing myoclonic jerks and GTCs, but became seizure-free on LCM; the oldest discontinued due to AEs not related to seizure aggravation. Similarly Zangaladze et al. reported the case of a 21-year-old with JME who was experiencing daily myoclonic jerks and GTCs who became seizure-free after addition of LCM.[41] In the studies with adults, case reports described exacerbation of myoclonus in two patients with JME[47,48]; however, in the remaining cases, treatment with LCM was associated with a reduction in seizure frequency. In patients with other seizure types, LCM appeared to be beneficial in most. Results of a Phase II trial, conducted with specific focus on assessment of absence and myoclonic seizure frequency, did not reveal a systematic worsening of these seizures, in either the main trial or the extension, with up to 12 months of exposure.[43]

Given the small numbers of patients with PGE identified in this review, evidence for the feasibility of extrapolation is not

as clear cut as it in focal epilepsy. In terms of GTC and myoclonic seizures, data could be extrapolated, as these share similar electro-clinical expression and pathophysiology independently of the syndromic setting. According to PEACE, evidence so far indicates that extrapolation in GTCs is reasonable, since these typically start occurring after the age 2 years and have similar semiology to those occurring in adolescents and adults.[4] In the studies reviewed here, LCM showed benefit in the treatment of most children and adults experiencing GTC and myoclconic seizures. While there were reports of seizure aggravation, these were not consistent and in many cases, could not be clearly be attributed to LCM in the absence of control groups. Indeed, as noted by Sanmarti et al., who reported aggravation in 14.7% (n = 28/191) of patients, the highest in all studies, a causal link to LCM could not be demonstrated.[28] Importantly, not all patients with seizure aggravation discontinued treatment. Since data on aggravation of generalized seizures are typically based on anecdotal case reports or series, interpretation of data from such uncontrolled and retrospective studies, and particularly of case reports, must be made with caution.[60]

In terms of safety and tolerability, with the exception of safety case reports, LCM was described as being well tolerated by patients in most studies. Common AEs included those observed in the adult population, such as dizziness, headache, somnolence/drowsiness, vomiting, nausea, blurred vision and diplopia. Behaviour- or mood-related AEs were also noted in some studies, using terminology such as nervousness, hyperactivity, irritability, restlessness and worsening behaviour. Such AEs are not unexpected given the high prevalence of behavioural and psychiatric comorbidities among children with epilepsy. These comorbidities can affect up to 50% of children, with higher rates reported among those with intellectual disability.[62] In a study by Pasha et al., behaviour was evaluated objectively, and was shown to have improved after 3 months' treatment with LCM.[26] A case of a 5-year old girl who developed behavioural problems after taking LCM (100 mg/day for 1 week) was also reported by the same group.[25] After persisting with treatment for 4 weeks, LCM was stopped and the child's behaviour returned to 'normal'. Depression associated with suicidal ideation was reported in a 17.5-year old, who was being treated with LCM 400 mg/day (6 mg/kg daily); the thoughts subsided after discontinuation.[23] Pancytopenia was reported in a child with history of blood count disturbances before LCM initiation. Following a re-challenge with LCM 2 months later, the patient remained seizure-free up to study end (16 months) with normal haematology examinations.[22] Finally, a case of oral tics was reported in one child that subsided after LCM discontinuation.[23] Discontinuations due to AEs ranged from none in four studies to 25% (four of 16 patients) in one study.

No cardiovascular AEs clearly attributable to LCM were reported in the studies. Wide complex tachycardia was described in a case report of a 3-year old who was taking the antiarrhythmic drug flecainide and had received two 50 mg doses of LCM 4 h apart.[63] The episode resolved after withdrawal of both drugs. It must be noted that LCM should be used with caution in patients treated with class I antiarrhythmics.[64,65] Tachyarrhythmia, as part of multi-organ failure and persistent SE that led to death, was described in a case report of a 3-year old (full details of both cases provided in Supplementary material).[66] A death was also noted in the patient flow figure in the study by Sanmarti et al.[28] The death occurred in a child suffering from severe cerebral palsy for reasons independent of epilepsy (personal communication from author).

Lacosamide was typically initiated at a dose of 1–3 mg/kg/day in paediatric studies, reaching mean maintenance doses of 4.1–15.1 mg/kg/day. High mean doses (>12 mg/kg/day, corresponding approximately to >600 mg/day adult dose) were used in four studies; those by Grosso et al. that included patients with LGS only,[37] with CSWS[42] and very young children (2–4 years)[17] and the study by Heyman et al.[33] The use of high doses in three of these studies reflect disease severity, while in the fourth,[17] it was most likely required due to increased drug clearance in very young children. Mean maintenance dose was considerably lower in most other studies. The maximum dose identified was 25.1 mg/kg/day, reported by McGinnis and Kessler; in this study, the median highest dose was 6.6 mg/kg/day (range 1.4–25.1 mg/kg/day).[27] None of the studies reported LCM serum levels, which could help in making the 'pharmacologic bridge' to adult studies and assessing efficacy.

The limitations of this systematic review are clear—as with any such review, results depend on the quality of the studies included. Many of the studies were retrospective, or case reports with 1–3 patients only. While assessment of the safety profile is more straightforward, assessment of seizure outcomes is hindered by the differences in study type (prospective or retrospective), the interval at which assessments were made (exposure duration) and epilepsy/seizure type (focal or generalized). A weakness of some studies that included mixed populations is that corresponding syndromic diagnoses were not systematically provided, which may bias the interpretation of efficacy. For example, GTC seizures in a patient with JME may not exactly correspond, from a pathophysiological viewpoint, to those in a patient with LGS. Therefore, when efficacy per seizure type is discussed in studies with grouped results, response of the same seizure type in a given syndromic category should ideally also be provided. Conducting trials with patients with only one generalised seizure type, or a specific epilepsy syndrome could also be considered.

5. Conclusions

In this review, use of LCM in children ranging in age from 6 months to 21 years, and including many with severe epilepsies of variable aetiology, was well tolerated and associated with AEs generally already reported in adults. In one study with both paediatric and adult patients, investigators reported no significant differences in the incidence of AEs between the two groups.[31]

In focal epilepsy, findings from open-label studies in children corroborated those of RCTs conducted with both adult and paediatric patients, supporting the feasibility of extrapolating efficacy results from adults to children ≥4 years of age, which is now accepted by regulatory authorities. Evidence for generalised epilepsies was not as strong, due to the overall small number of patients, whether adult or paediatric. This

observation confirms that RCTs in these populations remain problematic, and highlights the importance of studies conducted in the real-life setting. Such studies, particularly in children with severe childhood-onset epilepsies, offer a unique opportunity for large-scale screening, looking for efficacy clues against various seizures types that can subsequently lead either to controlled trials or, where applicable, to extrapolation. They also provide important safety data in rare and complex epilepsies. Finally, the importance of including the syndromic diagnosis (and for those not diagnosed to group them as unclassified) and analysing efficacy results not only per generalized seizure type but also per syndrome, particularly for young children, must be highlighted.

Conflict of interest

Ahinee Anamoo, Ali Bozorg, Maureen Cooney, Linda Kalilani, and Christine Taeter are current employees of UCB Pharma. Amanda Golembesky is a former employee of UCB Pharma and now based in Boehringer Ingelheim International GmbH, Ingelheim am Rhein, Germany. Azita Tofighy, who received funding from UCB Pharma for writing the manuscript, is a former employee of UCB Pharma. Alexis Arzimanoglou and James Wheless have received funding from UCB Pharma for research and attending scientific meetings and advisory boards.

Research data sharing

No novel, unreported data were generated in this study. Spreadsheets detailing inclusion/exclusion of reports identified in literature searches will be made available on request.

Acknowledgments

The authors acknowledge the contribution of Barbara Pelgrims, PhD (UCB Pharma, Brussels, Belgium) in overseeing the development of the manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejpn.2019.05.002.

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