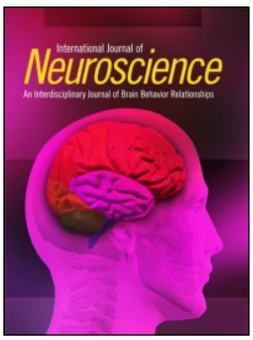

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ORIGINAL ARTICLE

Initial monotherapy with eslicarbazepine acetate for the management of adult patients with focal epilepsy in clinical practice: a meta-analysis of observational studies

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ABSTRACT

Aim of the study: To assess the effectiveness, overall tolerability of eslicarbazepine acetate (ESL) as an initial or early monotherapy treatment of adult patients with focal epilepsy under real-world practice conditions.

Materials and methods: We focused on real-world longitudinal studies that included or separately reported the results of at least one of the efficacy outcomes of interest. A DerSimonian-Laird random effects model was used with the presentation of the 95% confidence intervals of the estimate

Results: 5 studies met our selection criteria and were included in the quantitative synthesis. All studies were observational and uncontrolled studies, and all but one were retrospective studies. The pooled proportion of patients who were seizure-free for the entire study period was 64.6% (95% CI, 45.7 to 79.8) at month 6 and 56.6% (95% CI, 50.2 to 62.8) at month 12. Pooled retention rates were 95.0% (95% CI, 90.3 to 97.5) at 6 months and 83.6% (95% CI, 73.9 to 90.1) at 12 months. The pooled proportion of patients who reported at least one adverse event was 27.2% (95% CI, 21.7 to 33.6), and the pooled proportion of patients who discontinued ESL due to adverse events was 8.9% (95% CI 6.2 to 12.6).

Conclusions: Our results suggest that initial or early monotherapy with ESL is effective and well-tolerated for the management of adult patients with focal epilepsy in clinical practice, with results that are at least similar to those reported in the pivotal randomized clinical trial of ESL monotherapy. No new safety signals with ESL have been identified in this systematic review.

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Introduction

The goals of treatment in patients with newly diagnosed epilepsy are to achieve seizure freedom with minimal adverse events. To this end, antiseizure medication (ASM) monotherapy is advocated [1,2]. In addition to improved tolerability with similar efficacy, the advantages of monotherapy over polytherapy include a reduced risk of drug interactions, seizure aggravation, the occurrence of comorbid depression, and noncompliance [1]. ASM monotherapy also appears to be associated with a greater quality of life [3], another key treatment goal.

Eslicarbazepine acetate (ESL) is a ASM of the dibenzazepine carboxamide family that inhibits voltage-gated sodium channels [4]. ESL (Zebinix® in non-US countries, and Aptiom® in the US) was first approved for the adjunctive treatment of adults with partial seizures (currently called focal-onset seizures) and, more recently, as monotherapy for that population. The efficacy of ESL monotherapy in patients with newly diagnosed focal-onset seizures is based on the results of a randomized, double-blind, multicenter study that demonstrated the noninferiority of once-daily ESL compared to twice-daily controlled-release carbamazepine in terms of seizure freedom for the entire 6-month evaluation phase; retention rates were also similar for ESL and controlled-release carbamazepine [5]. Efficacy results with ESL were maintained during a 2-year open-label extension both in patients kept

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on ESL monotherapy and those who switched from controlled-release carbamazepine to ESL, with a good tolerability and safety profile [6]. Head-to-head comparisons of ESL monotherapy with other second- or third-generation ASMs are lacking; however, the result of a network meta-analysis that included 4 randomized trials comparing levetiracetam, zonisamide, lacosomide and ESL with controlled-release carbamazepine found no differences among the studied drugs in the 6- and 12-month seizure freedom rates [7]. ESL provides some advantages over some other ASMs, such as limited pharmacokinetic and pharmacodynamic interactions, a once-daily administration, and a potentially improved tolerability profile, more specifically regarding psychiatric and metabolic adverse reactions [8,9], that may contribute to enhanced treatment compliance [10].

Randomized controlled trials (RCTs) are the gold standard for establishing the effects and value of a new intervention because of their internal validity. However, RCTs may not fully elucidate the benefits of treatment in clinical practice [11] due to external validity limitations, which often arise when using strict eligibility criteria [12,13]. Globally, RCTs do not provide all the evidence necessary to guide the clinical practice of epilepsy management [12], and some authors advocate for obtaining a broader assessment of the drug's overall effectiveness, complementing the information from RCTs with 'real-world' studies [14,15]. These real-world studies also provide an opportunity to better evaluate outcomes such as treatment retention rates as a measure of treatment effectiveness, an outcome measure that combines the impact of treatment on terms of efficacy, tolerability and patients' preference [16]; this outcome in RCTs may be influenced by factors related to the experimental design such as the tight follow-up or the use of certain comparators [17].

The aims of this systematic review were to assess the effectiveness, overall tolerability and specific tolerability issues of ESL as initial or early monotherapy treatment of patients with focal epilepsy under real-world practice conditions.

Materials and methods

Eligibility criteria

Type of studies

We focused on real-world longitudinal studies, regardless of the study design. The following sources of real-world data information were accepted [18]: registries, databases, administrative data, electronic health records, medical chart review, and observational studies. We only included studies published in English. The protocol of this systematic review was not registered in a database.

Types of participants

The studies needed to include or separately report the results of at least one of the efficacy outcomes of interest (see below) for adult participants aged 18 years and older with a diagnosis of focal epilepsy.

Types of interventions

We selected studies reporting data from patients treated with ESL as initial, first-line or early monotherapy, either for the whole population or for a study subgroup. We considered initial, first-line or early monotherapy as defined by the study's investigators, and the definition employed was recorded as part of the study information. We did not include switching or conversion studies because these designs are potentially confounded by the effects of baseline drugs and comedication withdrawal [19].

Type of outcome measures

The efficacy outcomes of interest were the frequency of seizure freedom for the whole study period, the frequency of seizure freedom from the last visit, and the retention rate. These three outcomes, when available, were recorded at 6, 12, and 24 months. We selected these two outcome measures because seizure freedom is the recommended primary outcome for a clinical trial of ASM monotherapy; thus, for the European Medicines Agency, 'the primary efficacy variable should be based on the proportion of patients remaining seizure-free for at least six months' [20]. The retention rate is also considered a key efficacy endpoint in monotherapy trials [21] and an adequate outcome for evaluating clinical effectiveness [15,16].

Safety outcomes included the proportion of patients reporting adverse events, the proportion of patients discontinuing ESL because of adverse events, and the proportion of patients reporting hyponatremia, drowsiness/somnolence, dizziness, and fatigue; these adverse events were selected because they were those reported in common by all the studies reporting adverse events/reactions for the monotherapy group. However, we recorded information on the whole tolerability profile as reported in the individual studies, which were reported in a nonaggregate manner.

Search methods for study identification

The following databases were searched in May 2020 from inception by a medical information specialist (IS-A, see the acknowledgments): MEDLINE/Embase, Cochrane's database and ClinicalTrial.gov. The search

strategy for MEDLINE/Embase was eslicarbazepine:ab,ti AND (monotherap*:ab,ti OR alone:ab,ti OR singl*:ab,ti) NOT (child* OR 'adolescence'/exp OR child:ab,ti OR children:ab,ti OR adolescen*:ab,ti OR teenager*:ab,ti). Similarly, the Cochrane database was searched using the following strategy: eslicarbazepine in Title Abstract Keyword AND (monotherap* OR alone OR singl*) in Title Abstract Keyword NOT (child OR children OR adolescen* OR teenager*) in Title Abstract Keyword - (Word variations have been searched). Finally, ClinicalTrials.gov was also searched for ESL monotherapy studies.

Study selection

Two reviewers (SF and FR-V) determined the eligibility of studies based on the title/abstract of each study identified by the search. The reviewers discarded studies that clearly did not satisfy the inclusion criteria, and the full texts of the remaining studies were obtained. These two reviewers assessed all the initially selected complete articles/records and selected those that met the previously described eligibility criteria; doubts regarding whether an article met the criteria were solved by consensus between the two reviewers. If no agreement could be reached, then a third reviewer (RR) was involved in the assessment.

We did not anonymize the studies prior to the assessment.

Data extraction and management

Two reviewers (FR-V and RR) independently extracted data from the selected studies, each using a standard Microsoft Excel form. The two extraction forms were compared, and in cases of discrepancies, both reviewers discussed the specific difference to reach an agreement prior to entering data into the final tables. If no agreement could be reached, then a third reviewer (SF) was consulted.

As characteristics of the studies, we recorded information on the first author, year of publication, study design, country, funding source, time frame, study duration, criteria for the diagnosis of epilepsy and definition of monotherapy. We extracted the following information on the characteristics of the patients: age, sex, age of onset of epilepsy, type of epilepsy, etiology of epilepsy, disease duration, number of seizures at baseline, proportion of naïve subjects, number of previous ASMs, and starting and continuation dose of ESL. Information on the treatment outcomes (see section 'Type of outcome measures' above) was recorded, including the definition of seizure freedom and the criteria for hyponatremia.

Data synthesis

All response data were binary and underwent a logit transformation. A DerSimonian-Laird random effects model was used with the presentation of the 95% confidence intervals of the estimate. We also presented the number of events and the size of the treatment group.

The heterogeneity of each meta-analysis was established by the significance of Cochran's τ^2 and was quantified by I^2. Significant values of heterogeneity (i.e. $I^2 > 0.5$) indicated inconsistent (heterogeneous) results of the meta-analysis. In the presence of relevant heterogeneity, the results were analyzed by subgroup meta-analysis based on the type of population for the analysis of the efficacy outcomes: observed cases (OC) or imputed with the last observation carried forward (LOCF) approach.

The results of each meta-analysis are presented with forest plots of the global estimate for the binary outcome and their 95% confidence intervals.

Results

Study selection

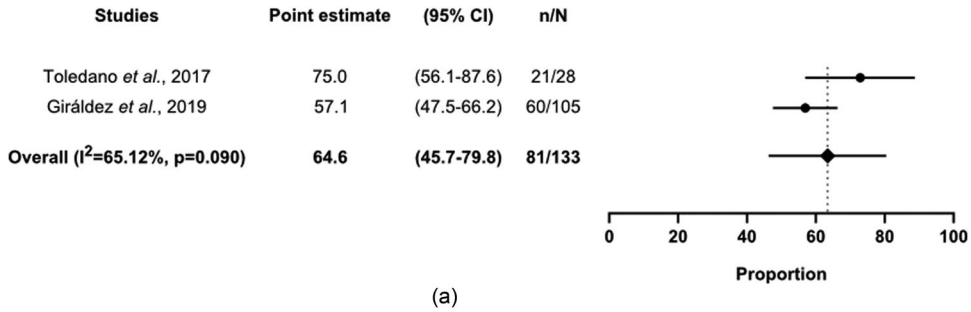
A total of 342 records were identified by the literature search: 199 in MEDLINE/Embase, 88 in Cochrane's database, and 55 in ClinicalTrials.gov. After revising the abstracts, the full texts of 24 records were retrieved and reviewed. Finally, 5 studies met our selection criteria and were included in the quantitative synthesis [22–26]. The study selection flow chart is presented in Supplementary Figure 1.

Study characteristics

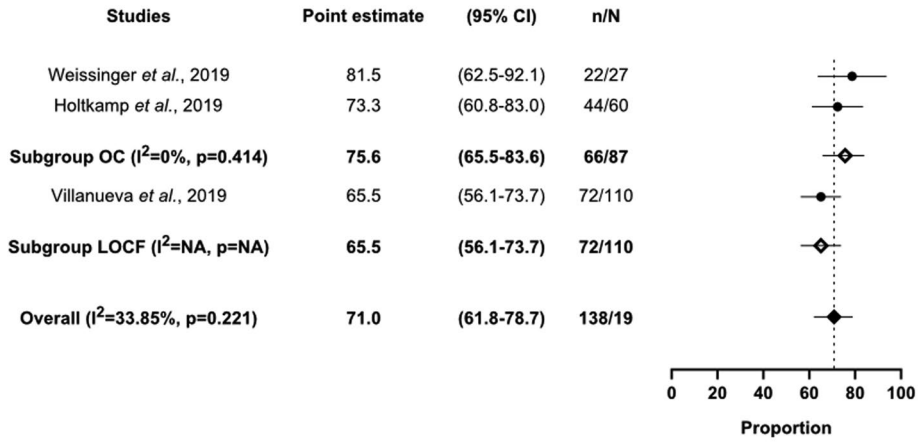
The 5 studies were published between 2017 and 2019, were multicenter and were conducted in Europe (3 in Spain, 1 in Germany, and 1 in several European countries) (Supplementary Table 1). All studies were observational and uncontrolled studies, and all but one were retrospective studies. The duration of studies varied from 6 months in the single prospective study [22] to a mean follow-up of 67 months in a longer study [26]. The definition of ESL monotherapy varied among studies (Supplementary Table 1).

Patients' characteristics

Overall, a total of 473 patients treated with ESL were included in this review. The characteristics of the patients of each individual study are presented in Table 1.



(a)



(b)

Figure 1. Proportion of seizure-free patients (6 months). (A) During the entire evaluation period, Toledano et al. [23] used an observed case analysis, while Giraldez et al. [24] used the method of Last Observation Carried Forward. CI, confidence interval; n, number of events; N, size of the treatment group. (B) From the prior visit. CI, confidence interval; LOCF, last observation carried forward; n, number of events; N, size of the treatment group; NA, not applicable; OC, observed cases

Note: Prior visit took place at least 3 months from this cutoff time period, except for Weissinger et al. [22], who included a single follow-up visit at approximately 6 months, and the follow-up period for this outcome comprised 3 months prior to the follow-up visit or the time period since baseline, whichever was shorter.

Patients were middle-aged and evenly distributed regarding sex except for the Giraldez et al. study, where over two-thirds of the patients were females [24]. Disease duration varies from a median of 0.9 months to a mean of 14 months, and the number of seizures also varies from a mean of approximately 1 to 5 per month. The proportion of ASM-naïve patients was over 65% in four studies [22–24,26], and 35% in one study [25].

Dose of eslicarbazepine acetate

The mean dose of ESL at 12 months was 781 mg/day in the Giraldez et al. [24] study and 895 mg/day in the Holtkamp et al. study [25]. When reported, the median dose of ESL at the last visit was 800 mg/day.

Risk of bias within studies

Since all studies were uncontrolled and descriptive in nature, we did not perform any evaluation of the risk of bias.

Synthesis of results

Seizure freedom

We found that all 5 studies reported seizure freedom at 6 months, 4 studies reported this outcome at 12 months, and a single study reported seizure freedom at 24 months.

In two studies, the authors reported seizure freedom at 6 months as the lack of seizures during the evaluated study period [23,24], and three studies reported it as the lack of seizures from the prior visit [22,25,26]. The pooled seizure freedom rate at 6 months as evaluated for the whole evaluation period was 64.6% (95% CI, 45.7 to 79.8) (Figure 1A), and for the studies evaluating it from the prior visit, it was 71.0% (95% CI, 61.8 to 78.7) (Figure 1B). Heterogeneity was not significant in either analysis but was lower when using the criterion based on the prior visit.

At 12 months, 3 studies reported the proportion of seizure-free patients for the entire evaluation period [23,24,26], and 3 studies reported seizure freedom from the prior visit [24–26], which in all cases corresponded to the previous 6 months. The proportion of seizure-free

Table 1. Characteristics of the study participants included in the meta-analysis.

First author, year	N	Age, mean (SD) [range]	Sex (%) males	Age of onset of epilepsy	Type of epilepsy	Etiology of epilepsy	Disease duration	Number of seizures, mean (SD) [range]	Number of previous ASMs	Starting dose (mg/d)	ESL dose (mg/d) mean (SD) & median [range]
Weissinger et al. 2019 [22]	35	54.5 (18.9) [NR]	60.0	NR	Simple partial seizures: 1.0 (mean) $n=28$, complex partial seizures: 2.2 (mean) $n=28$, secondarily generalized seizures: 0.4 (mean) $n=31$	Cerebrovascular disease (17.1%), brain tumor (14.3%), hippocampal sclerosis (0%), other cerebral pathology (11.4%) and not reported (57.1%)	Mean: 4.3 (8.7)	3.3 [0–48]	Mean: 0.4 [0–2] 74.3% no previous ASMs	NR	Target dose: mean 800.0 (137.2) Median: NR Last visit dose: mean 902.9 (280.2) Median: NR
Giráldez et al. 2019 [24]	106	45.6 (18.9) [NR]	68.9	Median: 38.5 [1.8–83.6]	NR	Cryptogenic (55.7%), symptomatic (40.6), idiopathic (3.8%)	Median: 1.4 [0.0–52.6]	1.12 (2.2)	0 (67.9%) 1 (32.1%)	NR	6 months: mean 781.1 (266.9) 12 months: mean 857.8 (271.9) Median (6 and 12 months): 800 [NR]
Holtkamp et al. 2019 [25]	88	41.2 (15.7) [14–79]	46.6	Mean: 27.9 (18.6)	Simple partial seizures: 15.7% $n=83$, complex partial seizures: 36.1% $n=83$, secondarily generalized seizures: 31.3% $n=83$, any partial seizure: 68.7% $n=83$	Structural-metabolic: 43.2% $n=81$, genetic: 4.9% $n=81$, unknow: 51.9% $n=81$	Mean: 13.4 (15.2)	5.2 (12.4)	Mean: 1.8 (2.2) 17/49 (34.7%) no previous ASMs	800 (253)	6 months: mean 900.0 (230.9); median: 800 [800–1600] 12 months: mean 895.2 (215.6); median: 800 [800–1600] Last visit: mean 1000.0 (315.6); median: 800 [400–1600]
Villanueva et al. 2019 [26]	127	49.1 [18–87]	50.4	Mean: 45.0 [4.4–86.9]	Focal aware seizure: 23.2% $n=112$, focal impaired awareness seizure: 40.2% $n=112$, focal to bilateral seizure: 42.9% $n=112$	Vascular: 15.7%, tumoral: 8.7%, mesial temporal sclerosis: 6.3%, cortical developmental malformation: 4.7%, cavernoma: 3.9%, trauma: 3.1%, perinatal anoxia: 0.8%, vascular malformation: 3.9%, infectious: 0%, other: 2.4%, unknown: 50.4% ($n=127$)	Median: 0.9 [0–34.1]	2.12 (5.1)	0 (82.7%) 1 (13.4%) 2 (1.6%) 3 (1.6%), ≥4 (0.8%)	NR	Mean: NR Median: 800 mg at all time points

Note: Toledano et al. [23] reported patient characteristics for the whole population but not for the monotherapy subgroup.
ASM, antiseizure medication; ESL, eslicarbazepine acetate; N, number of patients; NR, not reported; SD, standard deviation.

patients at 12 months for the entire study period was 56.6% (95% CI, 50.2 to 62.8), and these pooled results were not heterogeneous (Figure 2A). The pooled result when evaluated as seizure freedom from the last visit was 75.0% (95% CI, 59.2 to 86.2), but heterogeneity due to the type of analysis was large and significant (Figure 2B). The results for the subgroup of studies using an LOCF analysis were 68.0% (95% CI, 55.3 to 78.6).

We only found a study reporting seizure freedom at 24 months with a rate from the last visit of 61 out of 85 (71.8%) of the evaluable patients and a rate for the entire evaluation period of 47 of the 85 (55.3%) patients [26].

Retention rates

Retention rates were provided or could be calculated for 3 studies, 2 reporting data for 6 months [22,26] and 2 reporting data for 12 months [24,26].

Pooled retention rates were 95.0% (95% CI, 90.3 to 97.5) at 6 months and 83.6% (95% CI, 73.9 to 90.1) at 12 months, and heterogeneity was not significant in either outcome (Figure 3A,B).

One study provided data on retention rates at 24 months (105 out of 127 patients [82.7%]) [26].

Safety outcomes

Based on the results of 4 studies [22,24–26], the proportion of patients who reported at least one adverse

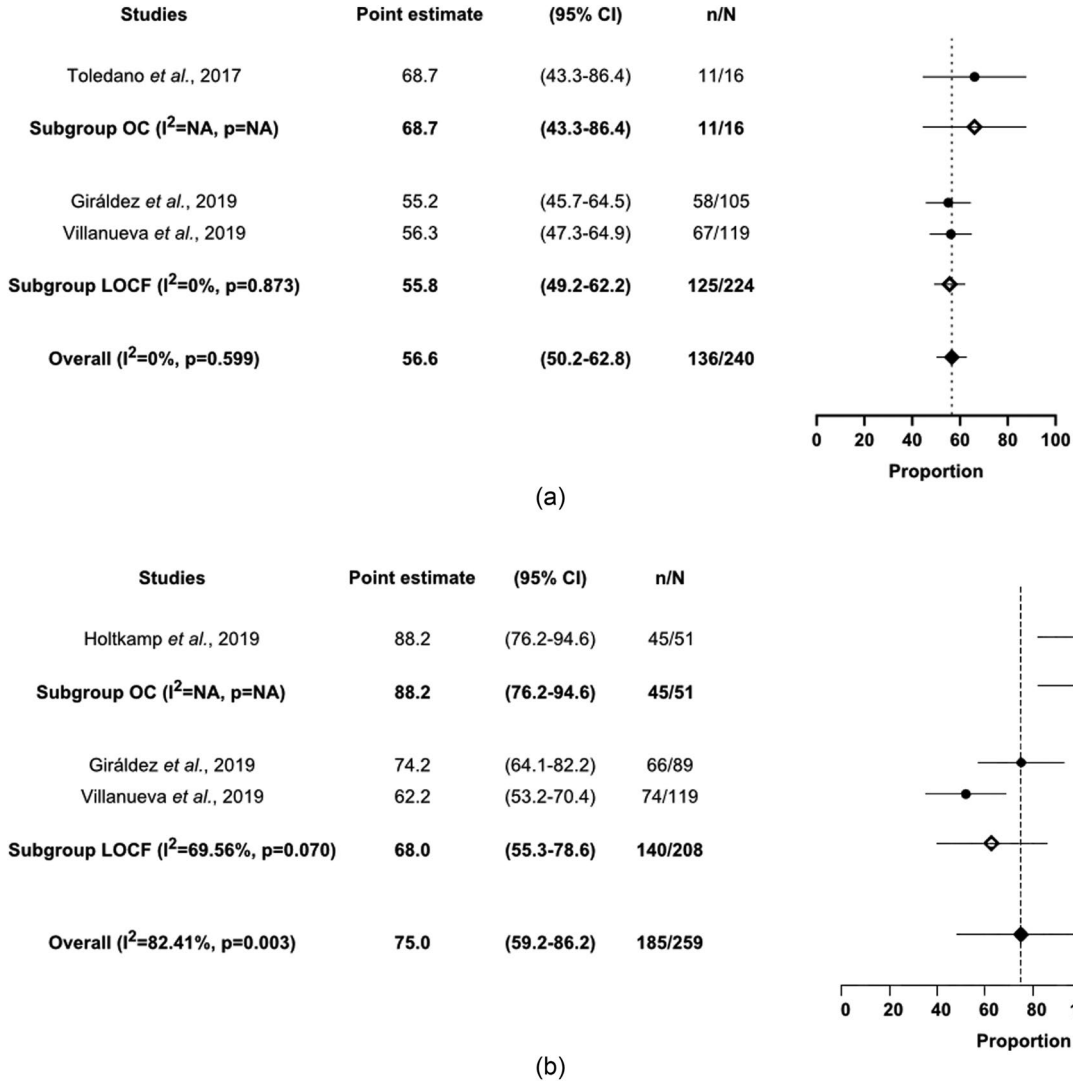


Figure 2. Proportion of seizure-free patients (12 months). (A) During the entire evaluation period. CI, confidence interval; LOCF, last observation carried forward; n, number of events; N, size of the treatment group; NA, not applicable; OC, observed cases. (B) From the prior visit. CI, confidence interval; LOCF, last observation carried forward; n, number of events; N, size of the treatment group; NA, not applicable; OC, observed cases.

Note: For these 3 studies, the prior visit took place at least 6 months from this cutoff time period.

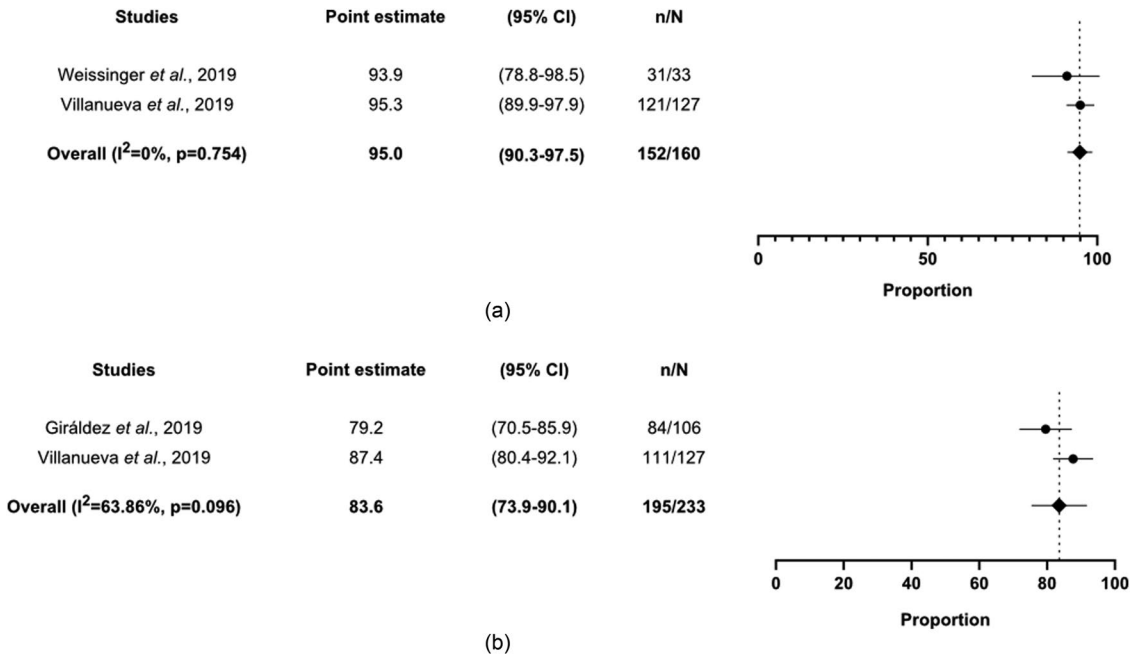


Figure 3. Treatment retention rates. (A) At 6 months. CI, confidence interval; n, number of events; N, size of treatment group. (B) At 12 months. CI, confidence interval; n, number of events; N, size of treatment group.

event was 27.2% (95% CI, 21.7 to 33.6), and pooling the results of three studies [24–26], the proportion of patients who discontinued ESL due to adverse events was 8.9% (95% CI 6.2 to 12.6), with low and nonsignificant heterogeneity in both outcomes (Supplementary Figures 2 and 3). Toledano et al did not report adverse events separately for the subgroup receiving ESL monotherapy [23].

The adverse events that were common to all 4 studies reporting tolerability data for the monotherapy group/subgroup were hyponatremia, somnolence, dizziness and fatigue [22,24–26]. The pooled proportion of patients exhibiting hyponatremia was 2.6% (95% CI, 1.0 to 6.4), with low and nonsignificant heterogeneity (Figure 4). The pooled frequency of drowsiness/somnolence was 6.5% (95% CI, 3.6 to 11.3), that of dizziness was 4.2% (95% CI, 2.0 to 8.7), and that of fatigue was 1.9% (95% CI 0.9 to 4.0), with low to moderate nonsignificant heterogeneity in all cases (Supplementary Figures 4A–C).

We present a summary of the most frequent (i.e. ≥1%) adverse events, as reported in the individual studies in Table 2. The frequency of ataxia was 0.9% in the Giraldez et al study [24], while Holtkamp et al. reported a frequency of instability/ataxia of 8.2% [25]. The frequency of rash was directly reported in two studies [24,25], with frequencies of 1.2% and 1.9%.

Discussion

The proportion of patients who were seizure-free in our study for the entire study period (65% at month 6 and 57% at month 12) was consistent with that reported in a previous RCT (71% and 64% at 6 and

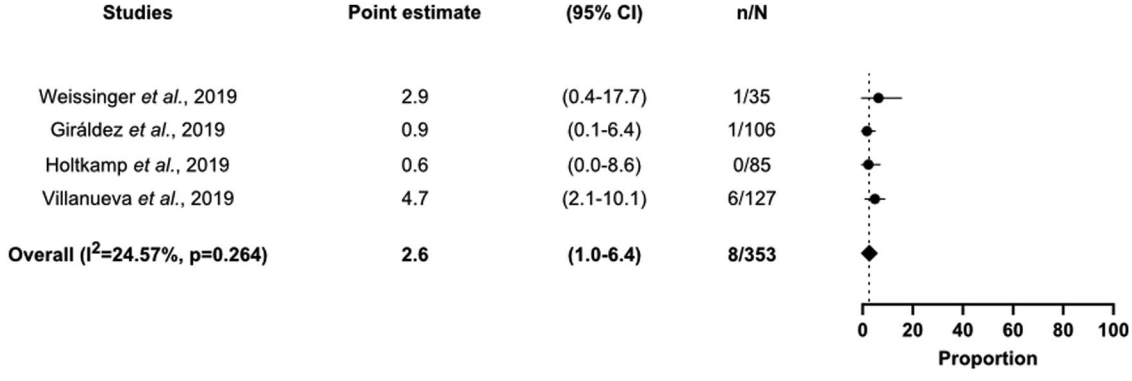


Figure 4. Frequency of hyponatremia. CI, confidence interval; n, number of events; N, size of the treatment group.

Table 2. Most frequent (≥1% in at least one study) adverse events with eslicarbazepine acetate.

Adverse event	Weissinger et al. 2019 [22], *N* = 35	Giraldez et al. 2019 [24], *N* = 106	Holtkamp et al. 2019 [25], *N* = 85	Villanueva et al. 2019 [26], *N* = 127
Criteria for reporting AEs in the article	**All AEs**	**≥2% and *n* ≥ 2 patients**	**≥5%**	***n* > 1 patients**
Somnolence	0.0	10.4	3.5	6.3
Instability/ataxia	–	0.9[a]	8.2[a]	–
Dizziness	0.0	7.5	1.2	3.9
Skin reactions	5.7[b]	–	–	–
Gastrointestinal	–	4.7[c]	–	1.6[d]
Hyponatremia	2.9	0.9	0.0	4.7
Headache	0.0	3.8	–	1.6
Depression	–	0.9	–	3.1
Nausea/vomiting	2.9	–	–	1.6
Attention difficulties	–	2.8	–	–
Memory disturbance	–	–	–	2.4
Fatigue	0.0	1.9	2.4	1.6
Rash	–	1.9	1.2	–
Anxiety	–	–	–	1.6
Irritability	–	–	–	1.6
Liver enzyme increase	–	––	–	1.6
Cholesterol increase	–	–	–	1.6

Note: Toledano et al. [23] reported adverse events for the whole population but not for the monotherapy subgroup.
[a]Ataxia was reported as "ataxia" by Giraldez et al. [24] and as "instability/ataxia" by Holtkamp et al. [25].
[b]Skin reactions were categorized using the Medical Dictionary for Regulatory Activities (MedDRA) by system organ class as skin reactions and subcutaneous disorders.
[c]Included nausea/vomiting and a miscellanea of symptoms.
[d]Excluded nausea/vomiting.

12 months, respectively) [5]. The slight numerical differences could be explained by the inclusion of the titration period in the observational studies, a period that was excluded in the clinical trial. Supporting this explanation, when evaluated as the seizure freedom from the prior visit (i.e. a period that excludes the titration period) our results (71% and 68% at 6 and 12 months, respectively, with the latter calculated using the more conservative LOCF approach) overlap with those of the clinical trial. In addition, we should bear in mind that the patients included in the clinical trial were younger with a much shorter duration of the disease (mean age at inclusion 37.6 years and age at diagnosis 37.3 years), while patients in these observational studies were between 41 and 56 years, and the duration of the disease ranged from 0.9 to 14.1 months. The median dose used at the last visit in the studies included in this review was 800 mg/day, which is in the lower limit of the target dose range recommended by the summary of product characteristics of ESL and consistent with the treatment dose where most patients remained in the pivotal study [5].

Although we did not find comparative studies, we do not expect relevant differences with other new ASMs. Both RCTs [7] and observational studies [27] have indicated that there are no substantial differences between ASMs in monotherapy in the rate of seizure freedom. Overall, it seems that the efficacy of new ASMs has not changed in recent decades, and differences among them are more related to their tolerability profile than to their effectiveness [28].

The treatment retention rate is considered a pragmatic treatment outcome that reflects the overall impact of treatment on the individual [16] and is therefore appropriate for real-world studies. As such, it is recommended that treatment effectiveness should be evaluated in patients with epilepsy [15,16], especially in patients receiving ASM monotherapy [21]. The pooled treatment retention rate in our meta-analysis was high at both 6 and 12 months (95% and 84%, respectively). In a pivotal study, Trinka et al. reported lower treatment retention during the 26-week evaluation period (71%) [5]. The expected effect of participating in a clinical trial on the retention rates would be the reverse [29]; we think these differences are likely to be related to the different characteristics of the population.

The proportion of patients reporting adverse events in our meta-analysis, despite the length of exposure being longer than in the pivotal trial, was low in comparison with the proportion reported in the pivotal clinical trial of ESL monotherapy. We should bear in mind that in observational studies, adverse events are underreported [30,31]. In addition, as Giraldez et al. highlight in their paper, it is also possible that tight dose schedules in RCTs lead to poorer tolerability compared with the more flexible dose adjustment used in

clinical practice [24]. On the other hand, length of exposure does not seem to be a critical factor for the tolerability of these drugs since most adverse events occurred during the first months of treatment [24,32]. In our view, withdrawals due to adverse events are a more interesting and comparable outcome between real-world studies and explanatory trials. Our pooled estimate of patients discontinuing ESL due to adverse events was 9%, lower than that reported in the pivotal clinical trial (14%). This positive result is consistent with the high retention rate found in our study and may be related to the individualized selection of patients and their management. The tolerability profile of ESL found in our systematic review of observational studies is consistent with that reported in clinical trials, including the ESL monotherapy trial, with somnolence, dizziness, headache and gastrointestinal adverse events as the most frequent adverse events. One study reported a somewhat high frequency of instability/ataxia; however, when evaluated as ataxia, the frequency of this adverse event was low.

Hyponatremia is an adverse event of special interest with carboxamides, although it appears more frequently associated with carbamazepine and oxcarbazepine than with ESL [33,34]. Although the studies included in our review included patients somewhat older than those included in the pivotal trial and that age is a risk factor for the occurrence of hyponatremia [33], we found a frequency of hyponatremia similar to that reported in the ESL monotherapy clinical trial (2.6% vs. 2.5%) [5]. Similarly, rash is also an adverse event of special interest. We did not meta-analyze outcomes related to rash, but the frequency of this adverse event in the 2 studies directly reporting this adverse event was relatively low (1.2% to 1.9%) and within the range reported in clinical trials (i.e. 0.5% with 400 mg, 1.2% with 800 mg and 3.2% with 1200 mg) [35] as well as within the range reported in a recent systematic review of ESL across all indications (1–4%) [36].

A limitation of this review is the heterogeneous definition of the ESL initial or early monotherapy group across studies. However, it is important to stress that in 3 studies, over two-thirds of the patients were treatment-naïve for any ASMs, and therefore, we could be considered it as ESL first-line monotherapy. All five studies were uncontrolled, which implies that we can only provide a picture of how ESL is working in the real world compared with how it worked in the pivotal RCT. The number of studies is small, which hinders the evaluation of heterogeneity; thus, although we only found statistically significant heterogeneity for a single outcome, the results in this regard should be interpreted with caution.

In conclusion, our results suggest that initial or early monotherapy with ESL is effective and well tolerated for the management of adult patients with focal epilepsy in clinical practice, with results that are at least similar to those reported in the pivotal RCT of ESL monotherapy, and similar to those obtained in other ASM monotherapy trials. No new safety signals with ESL have been identified in this systematic review.

Geolocation information

40.432692406845604, −3.657357786703153

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Data availability statement

This study was based on the data provided by the original studies included in this review. Data extraction forms are available from the corresponding author upon reasonable request.

Clinical trial registration

Not applicable.

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