



Effectiveness and Safety/Tolerability of Eslicarbazepine Acetate in Epilepsy Patients Aged ≥ 60 Versus < 60 Years: A Subanalysis from the Euro-Esli Study

Charlotte Lawthom · Pedro Bermejo · Dulce Campos · Rob McMurray · Vicente Villanueva

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ABSTRACT

Introduction: Clinical practice studies help guide antiepileptic drug (AED) therapy in patient groups routinely excluded from clinical trials, such as the elderly. The Euro-Esli study investigated the effectiveness and safety/tolerability of eslicarbazepine acetate (ESL) when used in everyday clinical practice in Europe. A subanalysis of data from elderly patients (≥ 60 years) included in the Euro-Esli study was conducted to assess these aspects of ESL use in this population.

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C. Lawthom (✉)
Aneurin Bevan University Health Board,
Royal Gwent Hospital, Newport, UK
e-mail: charlotte.lawthom2@wales.nhs.uk

P. Bermejo
Hospital Universitario Puerta de Hierro, Madrid,
Spain

D. Campos
Hospital Clinico Universitario, Valladolid, Spain

R. McMurray
Eisai Europe Ltd, Hatfield, Hertfordshire, UK

V. Villanueva
Hospital Universitario y Politécnico La Fe, Valencia,
Spain

Methods: Euro-Esli was a pooled analysis of 14 European clinical practice studies. Effectiveness parameters included responder ($\geq 50\%$ seizure frequency reduction) and seizure freedom rates after 3, 6 and 12 months of treatment and at last visit. Safety and tolerability were assessed throughout the follow-up by evaluating adverse events (AEs) and ESL discontinuation due to AEs, respectively. Data were compared for patients aged ≥ 60 versus those aged < 60 years at study entry.

Results: Euro-Esli included 2058 patients (mean age 44.0 years). Age at study entry was known for 2057 patients, of whom 358 (17.4%) and 1699 (82.6%) were aged ≥ 60 and < 60 years, respectively. Mean maximum ESL dose was 882.0 and 1008.2 mg/day in patients aged ≥ 60 and < 60 years, respectively ($p < 0.001$). At all timepoints, responder and seizure freedom rates were significantly higher in patients aged ≥ 60 versus < 60 years; for example, at 12 months, responder rates were 83.9 and 73.7%, respectively ($p = 0.002$), and seizure freedom rates were 58.5 and 37.1%, respectively ($p < 0.001$). The incidence of AEs was significantly higher in patients aged ≥ 60 versus < 60 years (41.4 vs. 32.5%; $p = 0.001$), but the rate of discontinuation due to AEs was comparable between age groups (16.2 vs 13.1%; $p =$ not significant). The safety/tolerability of ESL in patients aged ≥ 60 years was consistent with its known profile.

Conclusion: Eslicarbazepine acetate was efficacious and generally well tolerated when used to treat elderly patients with focal epilepsy in clinical practice, with no new or unexpected safety signals emerging in this setting.

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Keywords: Clinical practice; Elderly; Epilepsy; Eslicarbazepine acetate; Euro-Esli; Focal epilepsy; Focal seizures; Partial epilepsy; Partial seizures

INTRODUCTION

The prevalence and incidence of epilepsy are highest in the elderly population [1]. The occurrence of seizures in those aged > 60 years has been reported to exceed 100 individuals per 100,000 [2]. Indeed, after dementia and stroke, epilepsy is the third most common neurological disorder in the older age group [3]. Seizure aetiology in the elderly is often mixed, due to high levels of comorbidity. Risk factors associated with seizures and epilepsy in old age include, in particular, cerebrovascular disease and dementia (especially Alzheimer's disease), but also tumours (e.g. gliomas), metabolic and toxic causes (e.g. drugs and/or alcohol), head injury, subdural haematoma and infection [3]. In approximately 50% of elderly patients with epilepsy, the aetiology is unknown [4]. Partial seizures, with or without secondarily generalised tonic-clonic seizures, predominate in the elderly [2] (i.e. focal seizures, including focal to bilateral tonic-clonic seizures, according to the International League Against Epilepsy 2017 classification system [5]). Complex partial seizures (i.e. focal impaired awareness seizures [5]) are the most common seizure type [2]. Generalised-onset seizures are less common in the elderly than in younger patients [2].

Treating elderly patients with epilepsy is particularly challenging, not only due to high levels of comorbidity and associated polypharmacy, but also due to the impact of age-associated physiological changes on the pharmacodynamics and pharmacokinetics of antiepileptic drugs (AEDs) [6–9]. Furthermore, because elderly individuals are routinely

excluded from participation in clinical trials, information regarding the use of AEDs in this population is relatively scarce [10, 11]. Consequently, studies conducted under everyday clinical practice conditions provide a valuable source of evidence to help guide treatment decisions in this patient population.

Eslicarbazepine acetate (ESL) is a once-daily AED that is approved in Europe as monotherapy in the treatment of partial-onset seizures, with or without secondary generalisation, in adults with newly diagnosed epilepsy and as adjunctive therapy in adults, adolescents and children aged > 6 years with partial-onset seizures, with or without secondary generalisation [12]. In the USA, ESL is approved for the treatment of partial-onset seizures in patients aged ≥ 4 years [13]. One open-label, non-controlled trial evaluated the efficacy and safety/tolerability of ESL as adjunctive therapy in elderly patients (aged ≥ 65 years) with partial-onset seizures [14]. ESL was demonstrated to be efficacious in this trial and did not raise any major safety concerns [14]. However, further data from clinical practice are needed to complement these limited clinical trial data.

The Euro-Esli study investigated the effectiveness, safety and tolerability of ESL when used under everyday clinical practice in Europe [15]. Since Euro-Esli included a substantial number of elderly patients (aged ≥ 60 years), a subanalysis was conducted in order to provide further evidence of the use of ESL in this age group.

METHODS

Study Design

The Euro-Esli study was an exploratory, retrospective, pooled analysis of data from 14 European clinical practice studies, the full details of which were published in 2017 [15]. As a pooled analysis of previous studies, Euro-Esli was not registered. Effectiveness was assessed after 3, 6 and 12 months of ESL treatment and at final follow-up ('last visit'), and safety and tolerability were assessed for the duration of ESL treatment. A subanalysis was conducted of data from

patients aged ≥ 60 years at study entry. These data were compared with those from patients aged < 60 years at study entry.

The study protocol was approved by the Ethics Committee of Hospital Universitario y Politécnico La Fe, Valencia, Spain [15]. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Study Population

The studies included in Euro-Esli employed broad inclusion and exclusion criteria in order to be representative of the broad range of patients encountered in clinical practice [15]. This subanalysis included all patients from Euro-Esli for whom the age at study entry was known.

Study Assessments

Effectiveness assessments comprised the rate of response to ESL treatment, rate of seizure freedom and rate of retention on ESL treatment. Response was defined as $\geq 50\%$ seizure frequency reduction from baseline (i.e. prior to ESL initiation), and seizure freedom was defined as having no seizures since at least the prior visit, which was either 3 or 6 months, depending on the timepoint at which seizure freedom was assessed. Retention on ESL treatment was assessed over the first 12 months of follow-up. The reasons for ESL discontinuation were recorded.

Safety was assessed by evaluating adverse events (AEs), and tolerability was assessed by evaluating the rate of ESL discontinuation due to AEs. AEs were classified using the Medical Dictionary for Regulatory Activities version 16.0 [16]. Certain AEs of special interest were also assessed; these were cognitive AEs (defined as ‘Disturbance in attention/concentration’, ‘Memory problems’, ‘Confusion’, ‘Cognitive

disturbance’, ‘Sedation’, ‘Encephalopathy’ and ‘Bradypsychia’) and hyponatraemia.

Statistical Analyses

Details of the statistical methodology employed in Euro-Esli have been published previously [15]. The safety population was defined as all patients who initiated ESL treatment, and the effectiveness population was defined as all patients who initiated ESL treatment and had at least one effectiveness assessment. Since there was heterogeneity in the objectives of the studies included in Euro-Esli, there was also heterogeneity in the information each study reported. In particular, for each assessment, data were not available for all patients at every timepoint. Missing data were not imputed, except in cross-sectional studies in which the data for the last visit were captured and included in the established cut-off points (3, 6 or 12 months). When the observation timepoint of a study did not match the established cut-off points, the following allocations were made: observations performed between 1.5 and < 4.5 months were allocated to the 3-month visit; those performed between 4.5 and < 9 months were allocated to the 6-month visit; and those performed between 9 and 15 months were allocated to the 12-month visit. A ‘final’ variable was also created, in which the last observation of each patient was included, independently of the timepoint when it occurred.

A descriptive analysis of quantitative and qualitative variables was performed [15]. For each variable, the total number of patients for whom the data in question were available was recorded, and this value was used as the denominator for analysis. Quantitative variables were described as mean, standard deviation, median, minimum and maximum values, together with the number of valid cases and confidence intervals (CIs) or interquartile range (25th–75th percentile). Qualitative variables (responder rate, seizure freedom rate, incidence of AEs, rate of discontinuation due to AEs) were described as means of absolute frequencies and percentages. In this subanalysis, demographic

and baseline characteristics were compared between patients aged ≥ 60 and < 60 years using the Student's *t* test, Mann–Whitney *U* test, or chi-squared test, as appropriate. Effectiveness, safety and tolerability assessments were compared between patients aged ≥ 60 and < 60 years using the chi-squared test. Time to ESL discontinuation was assessed using the Kaplan–Meier method, and the duration of ESL treatment was compared between patients aged ≥ 60 and < 60 years using the log-rank test. The proportion of patients who discontinued ESL treatment was compared between patients aged ≥ 60 and < 60 years using the chi-squared test. Variation in ESL dose between baseline and the last visit in each subgroup was assessed using Student's *t* test, and ESL dose levels were compared between patients aged ≥ 60 and < 60 years using the Mann–Whitney *U* test. Variation between the initial and final number of concomitant AEDs used in each subgroup was assessed using the Wilcoxon signed-rank test, and the number of concomitant AEDs used was compared between patients aged ≥ 60 and < 60 years using the Mann–Whitney *U* test. The Statistical Package for the Social Sciences version 19.0 (IBM Corp., Armonk, NY, USA) was used for all analyses, and the significance level was 5% [15].

RESULTS

Patients

The Euro-Esli study included a total of 2058 patients (age range 14–88 years; mean age 44.0 years; 52.1% male) [15]. Age at study entry was known for 2057 patients, of whom 358 (17.4%) were aged ≥ 60 years and 1699 (82.6%) were aged < 60 years. Demographic and baseline characteristics of patients aged ≥ 60 and < 60 years are outlined in Table 1.

Age at onset of epilepsy was significantly higher in patients aged ≥ 60 versus those aged < 60 years (mean age 44.0 vs. 18.9 years; $p < 0.001$), although duration of epilepsy was similar between groups (mean duration 25.0 vs. 20.1 years, respectively; $p =$ not significant). Aetiology differed significantly between groups

Table 1 Demographic and baseline characteristics of patients aged ≥ 60 and < 60 years, respectively, at study entry

Patient characteristics	Age class of patients		<i>p</i> value
	≥ 60 years	< 60 years	
Baseline demographics			
Age (years)			
<i>N</i> ^a	358	1699	
Mean (SD)	68.9 (7.0)	38.8 (11.2)	< 0.001
Median (range)	67.0 (60.0–88.0)	38.9 (14.0–59.6)	
Sex			
<i>N</i> ^a	358	1698	
Male, <i>n</i> (%)	200 (55.9)	871 (51.3)	NS
Female, <i>n</i> (%)	158 (44.1)	827 (48.7)	
Epilepsy-related characteristics			
Age at onset of epilepsy (years)			
<i>N</i> ^a	327	1534	
Mean (SD)	44.0 (25.7)	18.9 (14.0)	< 0.001
Median (range)	52.0 (0.0–87.0)	16.2 (0.0–59.0)	
Duration of epilepsy (years)			
<i>N</i> ^a	327	1534	
Mean (SD)	25.0 (24.1)	20.1 (14.0)	NS
Median (range)	16.0 (0.0–81.8)	19.0 (0.0–58.8)	
Aetiology ^b			
<i>N</i> ^a	287	1368	
Structural/metabolic, <i>n</i> (%)	193 (67.2)	753 (55.0)	
Genetic, <i>n</i> (%)	1 (0.3)	35 (2.6)	< 0.001
Unknown, <i>n</i> (%)	93 (32.4)	580 (42.4)	

Table 1 continued

Patient characteristics	Age class of patients		<i>p</i> value
	≥ 60 years	< 60 years	
Baseline seizure type			
Any partial seizure			
<i>N</i> ^a	342	1648	
<i>n</i> (%)	313 (91.5)	1539 (93.4)	NS
Simple partial seizures			
<i>N</i> ^a	318	1515	
<i>n</i> (%)	67 (21.1)	410 (27.1)	0.027
Complex partial seizures			
<i>N</i> ^a	318	1515	
<i>n</i> (%)	198 (62.3)	938 (61.9)	NS
Secondarily generalised seizures			
<i>N</i> ^a	318	1515	
<i>n</i> (%)	120 (37.7)	664 (43.8)	0.046
Baseline monthly seizure frequency			
Any partial seizure			
<i>N</i> ^a	313	1539	
Mean (SD)	8.7 (54.0)	14.6 (49.0)	< 0.001
Median (range)	2.0 (0.1–900.0)	3.3 (0.1–1230.0)	
Simple partial seizures			
<i>N</i> ^a	56	339	
Mean (SD)	23.0 (120.1)	13.2 (42.5)	0.031
Median (range)	1.7 (0.3–900.0)	3.0 (0.3–600.0)	
Complex partial seizures			
<i>N</i> ^a	175	804	
Mean (SD)	5.7 (23.4)	8.8 (21.8)	< 0.001
Median (range)	1.7 (0.2–300.0)	3.0 (0.2–300.0)	

Table 1 continued

Patient characteristics	Age class of patients		<i>p</i> value
	≥ 60 years	< 60 years	
Secondarily generalised seizures			
<i>N</i> ^a	98	527	
Mean (SD)	0.9 (1.1)	2.8 (6.7)	< 0.001
Median (range)	0.7 (0.1–6.0)	1.0 (0.1–70.0)	
Comorbidities			
Intellectual disability			
<i>N</i> ^a	149	803	
Yes, <i>n</i> (%)	7 (4.7)	101 (12.6)	0.005
Psychiatric comorbidity ^c			
<i>N</i> ^a	225	913	
Yes, <i>n</i> (%)	56 (24.9)	227 (24.9)	NS
Depression			
<i>N</i> ^a	224	910	
Yes, <i>n</i> (%)	27 (12.1)	114 (12.5)	NS
AED treatment			
Total number of previous AEDs			
<i>N</i> ^a	309	1504	
Mean (SD)	1.6 (2.4)	2.6 (3.0)	< 0.001
Median (range)	1.0 (0.0–14.0)	2.0 (0.0–15.0)	
Total number of concomitant AEDs			
<i>N</i> ^a	355	1689	
Mean (SD)	1.5 (0.9)	1.8 (1.1)	< 0.001
Median (range)	1.0 (0.0–5.0)	2.0 (0.0–6.0)	

Table 1 continued

Patient characteristics	Age class of patients		<i>p</i> value
	≥ 60 years	< 60 years	
Number of concomitant AEDs, <i>n</i> (%)			
<i>N</i> ^a	355	1689	
0	14 (3.9)	74 (4.4)	
1	221 (62.3)	748 (44.3)	NA
2	76 (21.4)	490 (29.0)	
3	30 (8.5)	251 (14.9)	
≥ 4	14 (3.9)	126 (7.5)	
Reason for ESL initiation			
<i>N</i> ^a	254	1075	
Lack of effectiveness, <i>n</i> (%)	172 (67.7)	810 (75.3)	
Adverse reaction, <i>n</i> (%)	51 (20.1)	136 (12.7)	0.006
Both, <i>n</i> (%)	18 (7.1)	94 (8.7)	
Other, <i>n</i> (%)	13 (5.1)	35 (3.3)	

AED Antiepileptic drug, *ESL* eslicarbazepine acetate, *NA* not assessed, *NS* not significant, *SD* standard deviation

^a Total number of patients for whom the data in question were available

^b International League Against Epilepsy 2010 classification

^c Including depression

^d Excluding concomitant AEDs

($p < 0.001$), with a higher proportion of patients aged ≥ 60 versus < 60 years having a structural/metabolic aetiology and a lower proportion of patients aged ≥ 60 versus < 60 years having a genetic aetiology. The baseline monthly seizure frequency of any partial seizure was significantly lower in patients aged ≥ 60 versus < 60 years (mean 8.7 vs. 14.6; $p < 0.001$), as were the baseline monthly seizure frequencies of complex partial seizures (mean 5.7 vs. 8.8; $p < 0.001$) and secondarily generalised seizures (mean 0.9 vs. 2.8; $p < 0.001$). However, the baseline monthly seizure frequency of simple partial seizures was

significantly higher in patients aged ≥ 60 versus < 60 years (mean 23.0 vs. 13.2; $p < 0.001$).

The proportion of patients with psychiatric comorbidity (including depression) was identical in patients aged ≥ 60 versus < 60 years (24.9% in both groups), and the proportion of patients specifically with depression was also similar between groups (12.1 vs. 12.5%, respectively; $p =$ not significant). By contrast, the proportion of patients with intellectual disability was significantly lower in patients aged ≥ 60 versus < 60 years (4.7 vs. 12.6%; $p = 0.005$).

The total number of previous AEDs used (excluding concomitant AEDs) was significantly lower in patients aged ≥ 60 versus < 60 years (mean 1.6 vs. 2.6; $p < 0.001$), as was the number of concomitant AEDs used (mean 1.5 vs. 1.8; $p < 0.001$).

ESL Treatment

Reasons for initiating ESL treatment differed significantly between groups ($p = 0.006$), with a higher proportion of patients aged ≥ 60 versus < 60 years initiating ESL due to an adverse reaction to prior treatment (20.1 vs. 12.7%) and a lower proportion initiating ESL due to lack of effectiveness of prior treatment (67.7 vs. 75.3%) (Table 1).

ESL dosing during the course of the study is summarised in Table 2. The dose of ESL at treatment initiation was similar for patients aged ≥ 60 versus < 60 years (mean 537.2 vs. 527.1 mg/day; $p =$ not significant). However, at all other timepoints, the doses of ESL used were significantly lower in patients aged ≥ 60 versus < 60 years. For example, at the last visit, the mean ESL dose was 872.9 mg/day in patients aged ≥ 60 years versus 999.6 mg/day in those aged < 60 years ($p < 0.001$). Overall, the mean maximum ESL dose used was 882.0 mg/day in patients aged ≥ 60 years versus 1008.2 mg/day in those aged < 60 years ($p < 0.001$).

The number of concomitant AEDs used decreased significantly from baseline to last visit in both patients aged ≥ 60 years ($p < 0.001$) and in those aged < 60 years ($p < 0.001$). As with the number of concomitant AEDs used at baseline (Table 1), the number of concomitant AEDs used at the last visit was significantly

Table 2 Eslicarbazepine acetate dosing in patients aged ≥ 60 and < 60 years, respectively, at study entry

ESL dosing	Age class of patients		<i>p</i> value
	≥ 60 years	< 60 years	
ESL dose at treatment initiation (mg/day)			
<i>N</i> ^a	179	641	
Mean (SD)	537.2 (242.4)	527.1 (250.6)	NS
Median (range)	400.0 (150–1200)	400.0 (150–1600)	
ESL dose at 3 months (mg/day)			
<i>N</i> ^a	177	751	
Mean (SD)	800.0 (266.3)	891.1 (268.9)	< 0.001
Median (range)	800.0 (400–1600)	800.0 (400–2000)	
ESL dose at 6 months (mg/day)			
<i>N</i> ^a	192	828	
Mean (SD)	844.3 (267.6)	970.2 (292.5)	< 0.001
Median (range)	800.0 (200–1600)	800.0 (400–2800)	
ESL dose at 12 months (mg/day)			
<i>N</i> ^a	164	671	
Mean (SD)	897.6 (273.6)	1026.2 (307.2)	< 0.001
Median (range)	800.0 (400–1600)	1200.0 (400–2400)	
ESL dose at last visit (mg/day)			
<i>N</i> ^a	328	1591	
Mean (SD)	872.9 (311.4)	999.6 (328.1)	< 0.001
Median (range)	800.0 (200–2400)	800.0 (400–2800)	
Maximum dose (mg/day)			
<i>N</i> ^a	328	1591	
Mean (SD)	882.0 (307.3)	1008.2 (325.9)	< 0.001
Median (range)	800.0 (300–2400)	800.0 (400–2800)	

NS not significant, SD standard deviation

^a Total number of patients for whom data in question were available

lower in patients aged ≥ 60 versus < 60 years (mean 1.0 vs. 1.4; $p < 0.001$).

Effectiveness

At all timepoints, responder rates were significantly higher in patients aged ≥ 60 years versus those aged < 60 years (Fig. 1); for example, at

12 months, responder rates were 83.9 and 73.7% in patients aged ≥ 60 versus < 60 years, respectively ($\chi^2 = 9.33$; $p = 0.002$). Seizure freedom rates were also significantly higher in patients aged ≥ 60 versus < 60 years at all timepoints; for example, at 12 months, seizure freedom rates were 58.5 versus 37.1%, respectively ($\chi^2 = 31.16$; $p < 0.001$; Fig. 2).

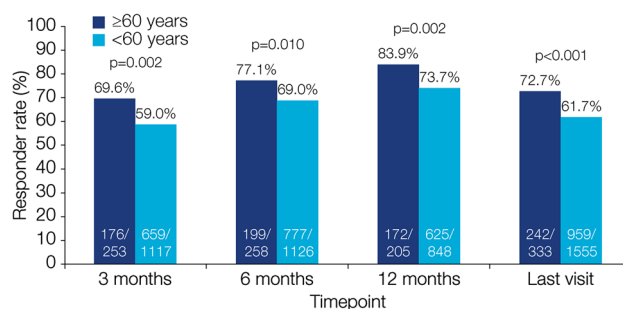


Fig. 1 Rate of response to treatment with eslicarbazepine acetate (responder rate) at 3, 6 and 12 months and at the last visit in patients aged ≥ 60 years versus those aged < 60 years at study entry. Response was defined

as $\geq 50\%$ reduction in seizure frequency from baseline. Statistical comparisons were conducted using the chi-squared test

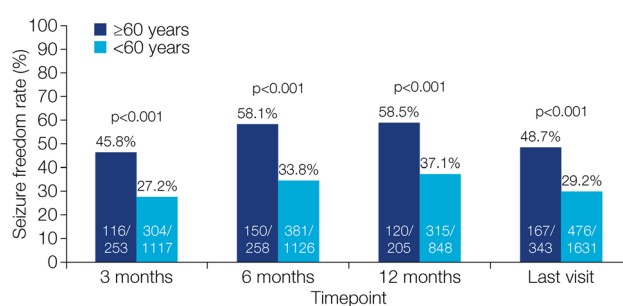


Fig. 2 Seizure freedom rate at 3, 6 and 12 months of treatment with eslicarbazepine acetate and at the last visit in patients aged ≥ 60 versus those aged < 60 years at

study entry. Seizure freedom was defined as no seizures since at least the prior visit. Statistical comparisons were conducted using the chi-squared test

Retention on ESL treatment over the first 12 months of follow-up was similar in patients aged ≥ 60 versus < 60 years ($p =$ not significant; Fig. 3). The mean duration of ESL treatment was 10.5 (95% CI 10.1–10.8) months in patients aged ≥ 60 years and 10.3 (95% CI 10.1–10.4) months in those aged < 60 years. The proportion of patients who discontinued ESL during the first 12 months of follow-up was 18.0% (63/350) in those aged ≥ 60 years and 21.1% (352/1667) in those aged < 60 years ($p =$ not significant). The reasons for ESL discontinuation primarily comprised lack of efficacy (2.0% in patients aged ≥ 60 years vs. 6.2% in patients aged < 60 years), adverse drug reaction (11.1 vs. 8.6%, respectively), or a combination of both (2.3 vs. 2.6%, respectively). The remaining patients who discontinued ESL treatment did so for ‘other’ (0.6% vs. 2.1%, respectively) or unknown (2.0% vs. 1.6%,

respectively) reasons. The most common ‘other’ reasons for discontinuing ESL treatment were request of the patient ($n = 1$) and lack of compliance ($n = 1$) in patients aged ≥ 60 years, and request of the patient ($n = 8$), cost ($n = 3$) and lack of compliance ($n = 1$) in patients aged < 60 years.

Safety and Tolerability

The overall incidence of AEs was significantly higher in patients aged ≥ 60 versus < 60 years (41.4 vs. 32.5%; $p = 0.001$; Table 3). The most frequently reported AEs in both treatment groups were dizziness, fatigue, somnolence and hyponatraemia. However, the rate of discontinuation due to AEs was comparable in patients aged ≥ 60 versus < 60 years (16.2 vs. 13.1%; $p =$ not significant). AEs that led to discontinuation in $\geq 2\%$ of patients aged ≥ 60 years were

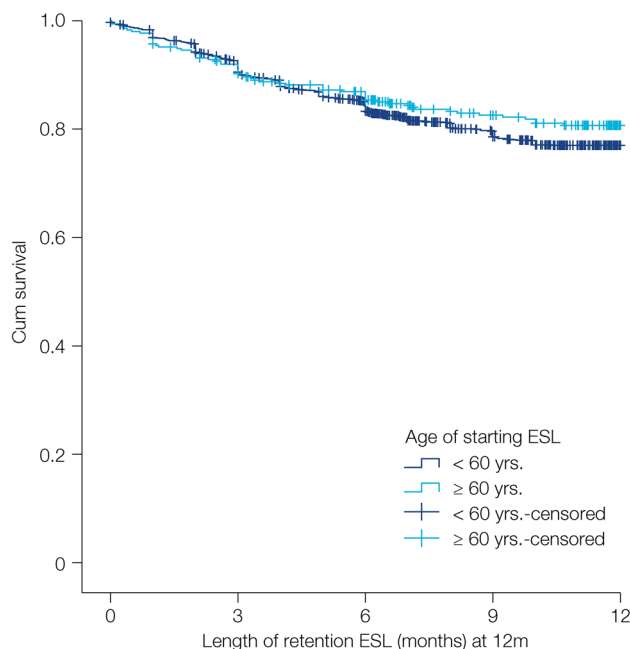


Fig. 3 Kaplan–Meier curve for retention on eslicarbazepine acetate (ESL) treatment over the first 12 months of follow-up

dizziness (4.0% vs. 2.1% in patients aged < 60 years), rash (2.7 vs. 1.3%, respectively), fatigue (2.1 vs. 2.0%, respectively) and hyponatraemia (2.1 vs. 0.8%, respectively).

The incidence of cognitive AEs was not significantly higher in patients aged ≥ 60 versus < 60 years (4.1 vs. 2.9%). The incidence of hyponatraemia was slightly higher in patients aged ≥ 60 than in those aged < 60 years (5.6 vs. 3.0%), as was the rate of ESL discontinuation due to hyponatraemia (2.1 vs. 0.8%). Concomitant medication (other than AEDs) was recorded for a total of 55 patients aged ≥ 60 years, of whom ten (18.2%) were treated with diuretics; none of these 55 patients developed hyponatraemia.

DISCUSSION

This subanalysis of data from the Euro-Esli study demonstrated that ESL is effective and generally well tolerated when used in clinical practice to treat focal epilepsy in patients aged ≥ 60 years. Responder and seizure freedom rates were significantly higher in patients aged ≥ 60 years than in those aged < 60 years at all timepoints. Although the incidence of AEs was significantly

higher in patients aged ≥ 60 versus < 60 years, the rate of ESL discontinuation due to AEs was comparable between groups, suggesting that ESL was not associated with intolerable AEs more frequently in elderly patients than in those of younger age. Retention provides a useful means of gauging the overall effectiveness and tolerability of a treatment, and retention on ESL treatment was higher in patients aged ≥ 60 versus < 60 years, although the difference was not statistically significant.

Although age at onset of epilepsy was significantly higher in patients aged ≥ 60 versus < 60 years, the duration of epilepsy was similar between groups. Moreover, patients aged ≥ 60 years were treated with significantly fewer prior AEDs and concomitant AEDs than patients aged < 60 years. Taken together, these findings may suggest that the elderly patients included in Euro-Esli predominantly comprised individuals who developed epilepsy in later life, rather than an aging population of patients who had developed epilepsy in earlier life. This possibility may be supported by the finding that the aetiology of epilepsy was significantly different between those aged ≥ 60 versus < 60 years; in particular, a structural/metabolic aetiology was more common in the

Table 3 Summary of adverse events in patients aged ≥ 60 and < 60 years, respectively, at study entry

Summary of AEs	Age class of patients	
	≥ 60 years	< 60 years
Patients with any AE		
<i>N</i>	353	1677
<i>n</i> (%)	146 (41.4)	545 (32.5)
<i>p</i> value	0.001	
Chi-squared value	10.20	
Most frequently reported AEs ^a		
<i>N</i>	340	1621
Dizziness, <i>n</i> (%)	30 (8.8)	102 (6.3)
Fatigue, <i>n</i> (%)	18 (5.3)	87 (5.4)
Somnolence, <i>n</i> (%)	26 (7.6)	74 (4.6)
Hyponatraemia, <i>n</i> (%)	19 (5.6)	49 (3.0)
Patients with any cognitive AEs ^b		
<i>N</i>	340	1621
<i>n</i> (%)	14 (4.1)	47 (2.9)
<i>p</i> value	NS	
Chi-squared value	1.38	
Patients with AEs leading to ESL discontinuation		
<i>N</i>	339	1620
<i>n</i> (%)	55 (16.2)	212 (13.1)
<i>p</i> value	NS	
Chi-squared value	2.35	
AEs most frequently leading to ESL discontinuation ^c		
<i>N</i>	328	1579
Dizziness, <i>n</i> (%)	13 (4.0)	33 (2.1)
Fatigue, <i>n</i> (%)	7 (2.1)	32 (2.0)
Somnolence, <i>n</i> (%)	4 (1.2)	25 (1.6)
Rash, <i>n</i> (%)	9 (2.7)	20 (1.3)
Instability/ataxia, <i>n</i> (%)	6 (1.8)	16 (1.0)
Diplopia/blurred vision, <i>n</i> (%)	5 (1.5)	17 (1.1)
Nausea, <i>n</i> (%)	3 (0.9)	18 (1.1)

Table 3 continued

Summary of AEs	Age class of patients	
	≥ 60 years	< 60 years
Disturbance in attention/concentration, <i>n</i> (%)	4 (1.2)	16 (1.0)
Hyponatraemia, <i>n</i> (%)	7 (2.1)	12 (0.8)

AE Adverse event, NS not significant

^a $\geq 5\%$ Patients in either group

^b Defined as 'Disturbance in attention/concentration', 'Memory problems', 'Confusion', 'Cognitive disturbance', 'Sedation', 'Encephalopathy' and 'Bradypsychia'

^c $\geq 1\%$ Patients in either group

elderly subgroup, consistent with the known risks of epilepsy associated with cerebrovascular disease, stroke and dementia in this age group [3]. It has also been suggested that a relatively minor metabolic insult in the elderly may elicit seizures from a pre-existing focus of injury [3].

The significantly greater effectiveness of ESL in patients aged ≥ 60 years versus those aged < 60 years—in terms of the observed rates of response and seizure freedom—was consistent with previous reports describing the superior effectiveness of AEDs in older versus younger patients with newly diagnosed epilepsy [17, 18], again supporting the surmise that the elderly patients included in Euro-Esli were treated relatively early in their disease course. Furthermore, the more favourable effectiveness observed in patients aged ≥ 60 versus < 60 years was achieved at significantly lower ESL doses and with significantly fewer concomitant AEDs in the former versus latter group, perhaps reflecting physiological differences between older and younger patients in terms of how AEDs are distributed, metabolised and cleared, possibly resulting in the achievement of therapeutic effects at relatively low doses [11].

The responder and seizure freedom rates observed in patients aged ≥ 60 years were higher than those reported by Costa et al. in their multicentre, open-label, non-controlled trial of ESL as adjunctive therapy in elderly patients with treatment-resistant focal epilepsy

[14]. In that trial, responder and seizure freedom rates at 26 weeks of ESL treatment were 54.9 and 15.5%, respectively [14], compared with 77.1 and 58.1%, respectively, at 6 months in the current analysis. Patients included in the Costa et al. trial [14] were somewhat older (mean age 71.6 years) than those included in the current subanalysis (mean age 68.9 years); they were also more likely to have been later in their disease course and/or more treatment resistant, since to qualify for inclusion they were required to have a documented diagnosis of epilepsy for ≥ 12 months and to have experienced at least two focal seizures during the 4 weeks prior to enrolment, while currently being treated with one or two AEDs [14]. By contrast, the Euro-Esli study did not employ such inclusion criteria, and the majority of patients (62.3%) were being treated with only one concomitant AED, with 3.9% of patients being treated with ESL as monotherapy. Since flexible dosing was employed in both studies, it is likely that the greater effectiveness of ESL in the current study, compared with the Costa et al. trial [14], may therefore be a consequence of the study population being earlier in their disease course and/or less refractory than the patients recruited for the Costa et al. trial.

In a retrospective survey of 29 patients with focal epilepsy aged > 65 years who were treated with ESL in clinical practice in Spain, responder and seizure freedom rates after 12 months of treatment were 62.1 and 24.1%, respectively [19]. These rates were considerably lower than the 12-month rates observed in the current subanalysis (83.9 and 58.5%, respectively), which may be due to 18 of the 29 patients being pharmacoresistant at baseline [19]. As in the current study, the authors of the Spanish audit note that the efficacy of ESL observed in elderly patients was not only greater than that observed in patients aged < 65 years (responder rates 62.1 vs. 48.8%, respectively), but was also achieved at a lower mean daily dose (850 vs. 1032.6 mg/day, respectively, at the end of follow-up) [19].

Several other AEDs have specifically been investigated in elderly patients in clinical trials, including carbamazepine, lamotrigine, levetiracetam, gabapentin, topiramate and

phenobarbital, and, where reported, seizure freedom rates after 52–58 weeks ranged from 24.1 to 64.3% [20–25]. There is also some limited evidence for the use of other AEDs in elderly patients in the clinical practice setting. A retrospective chart review of patients with focal epilepsy aged ≥ 65 years who were treated with lacosamide monotherapy reported 12-month seizure freedom rates of 68.0% when lacosamide was used as first-line monotherapy and 56.3% following conversion to monotherapy [26]. In a prospective audit of elderly and younger patients treated with perampanel over a period of 57 months, the rate of seizure freedom was significantly higher in elderly versus younger patients (35.0 vs. 13.8%; $p = 0.009$) [27]. Finally, in a prospective observational study of patients with late-onset (≥ 65 years) post-stroke seizures who were treated with levetiracetam for 18 months, the 12-month seizure freedom rate was 77.1% [28].

Although it is not feasible to make direct comparisons between investigations that are diverse in terms of design, study population and setting, it is noteworthy that, as in the current study, the effectiveness of AEDs in the clinical practice setting was, in general, somewhat better than the efficacy observed in clinical trials. This improved effectiveness is likely to reflect the individualised treatment approach employed in clinical practice, where patients are treated according to their specific needs, rather than according to a trial protocol-defined schedule. It is also notable that, in studies in which outcomes were reported for elderly and younger patients, AEDs were more effective in the former versus latter groups [19, 27], as was the case in the current study.

The higher incidence of AEs in patients aged ≥ 60 versus < 60 years in the current subanalysis is not unexpected, given the relatively high levels of comorbidities and comedications in elderly patients, together with age-related physiological changes, which increase the likelihood of drug–drug interactions, pharmacological alterations and associated drug toxicity [4, 11, 29–31]. It is therefore encouraging that tolerability (as assessed by evaluating ESL discontinuation due to AEs) was not significantly different between patients aged ≥ 60 and

those aged < 60 years. In addition, the incidence of cognitive AEs was not significantly higher in elderly patients than in those of younger age. Since patients aged ≥ 60 years often have significant cognitive impairments (such as memory loss) [32], it is reassuring that there was no evidence of ESL causing and/or exacerbating cognitive problems in the current study.

The elderly are at increased risk of developing hyponatraemia than are younger individuals, primarily due to age-related impairment in the capacity to excrete water and an increased likelihood of exposure to medications and comorbidities associated with hyponatraemia [33]. Furthermore, the symptoms and manifestations of hyponatraemia are more frequent and severe in the elderly, and hyponatraemia is independently associated with an increased risk of mortality in this age group [33]. Hyponatraemia has been reported to be a common AE in patients treated with ESL in clinical trials, occurring in 1.5% of patients overall [12], and higher rates have been reported in clinical practice studies [34, 35]. In the Costa et al. trial conducted in patients aged ≥ 65 years, hyponatraemia was reported as an AE and serious AE in 8.3 and 1.4% of patients, respectively, and led to ESL discontinuation in 4.2% of patients [14]. In the current subanalysis, hyponatraemia was reported as an AE in 5.6% of patients aged ≥ 60 years (vs. 3.0% in those aged < 60 years) and led to ESL discontinuation in 2.1% of patients aged ≥ 60 years (vs. 0.8% in those aged < 60 years). None of the patients treated with diuretics or other comedications developed hyponatraemia, although this information was only available for a relatively small subgroup of patients ($n = 55$). Although the rates of hyponatraemia observed in the current subanalysis were generally consistent with those reported previously, it is good practice to monitor for the potential development of hyponatraemia with ESL treatment, particularly in the elderly [36]. Overall, the safety and tolerability of ESL observed in the current study were consistent with its known profile [12], and no new or unexpected safety signals emerged in elderly patients treated in this clinical practice setting.

The study has a number of limitations because it was a subanalysis of a retrospective pooled analysis of studies that were heterogeneous in terms of objectives and designs [15]. Moreover, there was a lack of correction for multiple comparisons and, since the study was conducted under clinical practice conditions, it was essentially open-label in nature. Individual patient data were previously reviewed by the authors of the individual studies included in Euro-Esli, but they were not reviewed systematically post hoc [15]. As previously mentioned, the heterogeneous nature of the studies in Euro-Esli also meant that, across all endpoints and assessments, data were not available for all patients at all timepoints. In addition, concomitant medications were unknown in a large subset of patients. Nevertheless, Euro-Esli is the largest study of ESL in clinical practice conducted to date, and the number of elderly patients included in the study mitigate some of these limitations and allow meaningful assessments to be conducted.

CONCLUSIONS

This subanalysis of the Euro-Esli study demonstrated that ESL is an efficacious and generally well-tolerated treatment for elderly patients with focal epilepsy when used in clinical practice, with no new or unexpected safety signals emerging in this setting.

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Compliance with Ethics Guidelines. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Data Availability. The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

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