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Effectiveness of eslicarbazepine acetate in dependency of baseline anticonvulsant therapy: Results from a German prospective multicenter clinical practice study

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ABSTRACT

Eslicarbazepine acetate (ESL) is a third-generation antiepileptic drug (AED) approved as monotherapy for partial-onset seizures in adults and as adjunctive therapy in patients aged above 6 years in the European Union (EU). The prospective observational **Z**ebinix **E**ffects in **DE**pendency of **BA**seline **C**onditions (ZEDEBAC) study aimed at investigating the effectiveness of ESL in clinical practice, with ESL being administered as monotherapy (mono group), as only add-on to a current monotherapy (1+ group), or as add-on to ≥2 baseline AEDs (≥2+ group). In total, 237 patients were included, 35 in the mono group, 114 in the 1+, and 88 in the ≥2+ group. Six-month retention rates were 93.9%, 78.0%, and 75.3% in the mono, 1+, and ≥2+ group. There were 90.5%, 77.6%, and 48.3% of patients in the mono, 1+, and ≥2+ groups who were responders (patients with a ≥50% reduction in seizure frequency at follow-up vs. baseline). Seizure freedom rates were 81.5%, 47.9%, and 23.4%, respectively. Adverse drug reactions (ADRs) occurred in 11.4% of patients of the mono, 19.3% of the 1+, and 28.4% of patients of the ≥2+ group. Hyponatremia was reported as ADR in 3.4% of all patients. Although baseline variables differed considerably, with most elderly patients with tumor-related and vascular etiologies in the mono group and most patients with refractory epilepsies with pronounced use of concomitant sodium channel blockers (SCBs) in the ≥2+ group, retention as a measure of real-life effectiveness turned out not to be substantially different and favorable in all groups.

1. Introduction

Strategies of pharmacological epilepsy treatment have changed considerably within the past decades. Since anticonvulsant monotherapy replaced combination therapy as preferred treatment option for patients with epilepsy 50 years ago [1], monotherapy is still the strategy of choice for patients with newly diagnosed epilepsy because of reduced risks for drug–drug interactions, fewer adverse events (AEs), and better patient compliance [2,3]. With an increasing number of options for anticonvulsant monotherapy over the past decades, aspects like tolerability in different patient groups and the optimization of patients' individual quality of life (QoL) have gained importance when choosing a drug for monotherapy [4]. One of these groups of special interest are elderly patients, which often appear more sensitive to adverse drug reactions (ADRs) than younger patients [5,6].

With regard to add-on therapies, a range of newer antiepileptic drugs (AEDs) with improved interaction profiles became available in recent years [7], and the debate around consecutive mono- vs. early combination therapies has gained new momentum [8]. Since recently, the German epilepsy guidelines explicitly recommend early combination therapies after partly but insufficient response to the first monotherapy [9].

Abbreviations: 1+ group, patient group treated with ESL as only add-on to a current monotherapy; ≥2+ group, patient group treated with ESL as add-on to ≥2 baseline AEDs; ADR, adverse drug reaction; AE, adverse event; AED, antiepileptic drug; CBZ, carbamazepine; ESL, eslicarbazepine acetate; EU, European Union; ILAE, International League Against Epilepsy; LEV, levetiracetam; LTG, lamotrigine; MedDRA, medical dictionary for regulatory activities; mono group, patient group treated with ESL in monotherapy; OXC, oxcarbazepine; QOLIE-10, Quality Of Life In Epilepsy Inventory-10; SAE, serious adverse event; SCB, sodium channel blocker; SD, standard deviation; SmPC, summary of product characteristics; VPA, valproic acid; ZEDEBAC, **Z**ebinix **E**ffects in **DE**pendency of **BA**seline **C**onditions

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Combination therapy with two or more concomitant AEDs is a common therapeutic situation in patients with difficult-to-treat epilepsies [10,11]. Often, two drugs with different mechanism of action are combined, following a more or less implicit "rational polytherapy" approach. While controlled clinical trials investigating the benefits of specific AED combinations are rare [12], combining drugs like sodium channel blockers (SCBs) with similar mechanisms of action has been described as being associated with an increased risk of therapy failure [13].

Although drug regimens of three or more AEDs are generally discouraged, as they may not provide additional efficacy but an increased likelihood of tolerability issues and drug–drug interactions, these still represent a frequent condition in AED registration trials, and also a common situation in clinical practice, often as a result of initiating a third drug, with the intention to withdraw another later on, which was not put into practice [14,15]. In these complicated situations, the availability of AEDs with benign tolerability profiles in combination therapies is of high importance, as these may soften the negative impact of high drug loads [16].

Eslicarbazepine acetate (ESL, Zebinix®) is a third-generation sodium channel active drug, which was approved in the European Union (EU) in 2009 for the adjunctive treatment of partial-onset seizures in adult patients (since 2016 for patients aged above 6 years), and since April 2017, also as monotherapy for patients with newly diagnosed epilepsy with partial-onset seizures [17], based on positive phase III data [18,19]. As such, ESL is a potential therapy of choice for all of the above described scenarios, from monotherapy to late add-on treatment. Clinical data support the consistent tolerability profile of ESL in various patient populations and therapeutic settings, with dizziness, headache, fatigue, somnolence, and nausea being the leading AEs [18–20]. The retention rate of ESL, a measure of effectiveness of a drug, combining efficacy and tolerability aspects [21], has been described as high as 73% after 12 months in a large pan-European data audit in >2000 patients with different degrees of treatment refractoriness [20].

Despite the rich practice-related data available for ESL, especially in adjunctive settings, there is no study to date that prospectively investigated treatment outcomes for patients with ESL in clinical practice considering different therapeutic conditions at baseline, as coded by number of AEDs. The **Z**ebinix **E**ffects in **DE**pendency of **BA**seline **C**onditions (ZEDEBAC) trial, a prospective observational study conducted in Germany, addressed this question by enrolling patients in different therapeutic conditions (ESL as monotherapy vs. only add-on vs. add-on to an existing polytherapy) over a follow-up period of 6 months, with the intention to describe and better understand the potentially different contributions of efficacy and tolerability to drug effectiveness in different patient populations.

2. Methods

The ZEDEBAC was a multicenter, noninterventional, prospective study. Adult patients with partial-onset seizures receiving ESL as monotherapy (mono group), as only adjunctive therapy to an AED monotherapy (1+ group), or as add-on to 2 or more AEDs (≥2+ group) were recruited at 43 study sites (tertiary epilepsy centers as well as general neurologist practices) from July 2015 to March 2018. Patients were assigned to one of the groups depending on the number of AEDs (excluding ESL) taken 31 days after baseline. If therapy with an AED was initiated (after the day of baseline visit) until 31 days after baseline, this was taken into account for group assignment. Likewise, if an AED taken at baseline was tapered off until 31 days after baseline, this was not taken into account for group assignment. This conversion period allowed for a more realistic representation of clinical practice than considering the number of AEDs at the day of baseline visit only. At study outset, it was planned to enroll 100 patients into each group. Seizures and epilepsies were classified in accordance with the terminology of the International League Against Epilepsy (ILAE) from 1981 to 1989 [22,23], as the study had been set up and had included the majority of patients before the new ILAE terminology was published in 2017 [24,25]. Only patients with a confirmed diagnosis of partial-onset seizures with or without secondary generalization were included. Patients were excluded if they had known psychogenic nonepileptic seizures, if they participated in another clinical trial, or had previously been included in the same study. As the study was noninterventional in nature, the clinicians' decision to prescribe ESL had to be made prior to and independent of the participation in the study. Administration of ESL was recommended to be in line with the summary of product characteristics (SmPC) [17]. Data were recorded at baseline and at a follow-up visit approximately after 6 months. Number and type of seizures during the last 3 months, dosing protocol of ESL (including target dose and time to reach target dose), concomitant AEDs, and number and type of AEs were recorded. Reasons for discontinuation of ESL therapy were collected as well. In addition, data on patient demographics, etiology, epilepsy duration, relevant comorbidities, previous AEDs, nonpharmacological therapies of epilepsy, and other concomitant medication were collected at baseline. The primary endpoint of the study was the retention rate after 6 months, defined as percentage of patients still on ESL therapy after this period. Secondary endpoints encompassed responder rate (percentage of patients showing a ≥50% reduction in seizure frequency at follow-up as compared with baseline), seizure freedom rate (defined as absence of any seizures at follow-up), and median percent change in seizure frequency, by seizure type, and for the total number of seizures (comparing the seizure frequencies at baseline and follow-up). Baseline was defined as the 3 months prior to inclusion, follow-up as the 3 months prior to the follow-up visit or the time period since baseline, whichever was shorter. To account for possible effects of follow-up durations of less than 90 days, sensitivity analyses were conducted. Incidence, type and severity of AEs, serious adverse events (SAEs), and the rate of discontinuations due to tolerability issues were assessed. In this report, we refer to ADRs where appropriate, i.e., AEs that were considered to be at least possibly related to ESL treatment by the investigator. Adverse events and ADRs were categorized by medical dictionary for regulatory activities (MedDRA) preferred terms, high-level group terms, or system organ class. Change in QoL was assessed by the Quality of Life in Epilepsy Inventory-10 (QOLIE-10) [26]. This paper–pencil test consists of 10 items regarding the patient's epilepsy-related QoL. Patients can choose from 4 to 6 response options resulting in a total score between 10 and 51. For ZEDEBAC, the scoring manual from the QOLIE-10-P was used, with QOLIE-10 score ranging from 0 to 100. Higher scores indicate an improvement in QoL. Cognitive functioning was assessed by the NeuroCogFX, a computer test addressing short-term memory, working memory, psychomotor speed, selective attention, verbal and figural memory as well as verbal fluency [27]. The average standard value is 100, standard deviation (SD) ± 10. Improvements in cognitive functioning are indicated by increased standard values. Descriptive analyses were performed separately for those patients treated with ESL in monotherapy (mono), as only add-on (1+), or as add-on to at least 2 AEDs (≥2+).

Written informed consent was obtained from all patients. The trial was conducted in accordance with the guidelines of the World Medical Association Declaration of Helsinki. Approval from the concerned regional Ethics Committees was obtained.

3. Results

3.1. Baseline characteristics

Two hundred and thirty-seven adult patients (45.6% female) were included in the study, 35 into the mono, 114 into the 1+, and 88 into the ≥2+ group. Patient demographics and baseline characteristics are presented in Table 1. Gender distribution was slightly in favor of male patients in mono and +1 group, and balanced in the ≥2+ group. Patients in the mono group were on average 54.5 years old, compared with 51.6 years in the 1+ and 45.1 years in the ≥2+ group, with most patients treated in tertiary epilepsy centers or epilepsy outpatient

Table 1
Patient demographics and baseline characteristics.

Characteristics	Mono group (n = 35)		1+ group (n = 114)		≥2+ group (n = 88)	
Gender						
Female, n (%)	14	(40.0)	48	(42.1)	46	(52.3)
Age						
N[a]	35		113		88	
Mean (SD), years	54.5	(18.9)	51.6	(19.0)	45.1	(15.6)
18–45 years, n (%)	11	(31.4)	45	(39.8)	42	(47.7)
46–64 years, n (%)	13	(37.1)	35	(31.0)	34	(38.6)
≥65 years, n (%)	11	(31.4)	33	(29.2)	12	(13.6)
Enrolled in tertiary epilepsy center/epilepsy outpatient clinic, n (%)	29	(82.9)	61	(53.5)	66	(75.0)
Duration of epilepsy						
N[a]	34		113		81	
Mean (SD), years	4.3	(8.7)	9.7	(11.6)	18.7	(15.5)
Etiology of patients with epilepsy-relevant finding in MRI (multiple answers possible), n (%)						
N[a]	15		75		52	
Cerebrovascular disease	6	(40.0)	24	(32.0)	12	(23.1)
Brain tumor	5	(33.3)	19	(25.3)	8	(15.4)
Hippocampal sclerosis	0	(0)	7	(9.3)	8	(15.4)
Other cerebral pathology[b]	4	(26.7)	28	(37.3)	25	(48.1)
Monthly seizure frequency during baseline period						
N[a]	26		109		76	
Mean (range)	3.3	(0–48)	5.7	(0–90)	11.2	(0–186)
N[a]	28		113		81	
Simple partial seizures, mean (range)	1.0	(0–9)	3.3	(0–90)	2.4	(0–40)
N[a]	28		111		86	
Complex partial seizures, mean (range)	2.2	(0–48)	1.7	(0–48)	7.9	(0–180)
N[a]	31		111		82	
Secondarily generalized seizures, mean (range)	0.4	(0–2)	0.5	(0–10)	0.5	(0–10)
Psychiatric comorbidity[c], n (%)	4	(11.4)	8	(7.0)	13	(14.8)
Number of previous AEDs						
Mean (range)	0.4	(0–2)	1.2	(0–10)	2.5	(0–11)
Most frequently used (>10% patients) previous AEDs						
Levetiracetam, n (%)	5	(14.3)	21	(18.4)	30	(34.1)
Carbamazepine, n (%)	4	(11.4)	18	(15.8)	26	(29.5)
Lamotrigine, n (%)	2	(5.7)	21	(18.4)	20	(22.7)
Valproic acid, n (%)	0	(0.0)	18	(15.8)	25	(28.4)
Oxcarbazepine, n (%)	0	(0.0)	14	(12.3)	25	(28.4)
Lacosamide, n (%)	0	(0.0)	10	(8.8)	18	(20.5)
Number of concomitant AEDs at baseline[d]						
Mean (range)	0.0	(0–1)	1.1	(0–2)	2.2	(1–4)
Most frequently used (>5% patients) concomitant AEDs during the study						
Levetiracetam, n (%)	1	(2.9)	68	(59.6)	46	(52.3)
Lamotrigine, n (%)	0	(0.0)	18	(15.8)	42	(47.7)
Valproic acid, n (%)	0	(0.0)	16	(14.0)	23	(26.1)
Lacosamide, n (%)	0	(0.0)	7	(6.1)	27	(30.7)
Zonisamide, n (%)	0	(0.0)	5	(4.4)	11	(12.5)
Carbamazepine, n (%)	0	(0.0)	7	(6.1)	8	(9.1)
Brivaracetam, n (%)	0	(0.0)	2	(1.8)	13	(14.8)

[a] N refers to the total number of patients for whom data in question were available.
[b] Other cerebral pathology was not defined in more detail.
[c] Psychiatric comorbidity was based on concomitant diseases classified in MedDRA system organ class "psychiatric disorders".
[d] Discrepancies between group assignment and number of AEDs at the day of baseline arise because of a conversion period of 31 days after baseline. MRI, magnetic resonance imaging.

clinics. The mean duration of epilepsy was 4.3 years (median 0.1) in the mono vs. 9.7 years (median 5.1) in the 1+ vs. 18.7 years (median 15.3) in the ≥2+ group. Cerebrovascular findings (40.0%) and tumors (33.3%) were the most frequent etiologies in the mono group, while hippocampal sclerosis was most frequent in the ≥2+ group (15.4%). At baseline, the monthly seizure frequency for all seizures was 3.3 in the mono, 5.7 in the 1+, and 11.2 in the ≥2+ group. For simple partial seizures, monthly seizure frequencies at baseline were 1.0, 3.3, and 2.4, respectively and 2.2, 1.7, and 7.9 for complex partial seizures. Regarding secondarily generalized seizures, the monthly seizure frequency at baseline was 0.4, 0.5, and 0.5 in the three groups.

3.2. AED treatment

In the mono group, 74.3% of patients had not received any other AED before, so ESL was prescribed as initial monotherapy. In the 1+ group, 42.1% of patients received AED monotherapy at the day of baseline and did not have any prior treatment, so ESL was added as first adjunctive treatment, 21.1% received AED monotherapy at the day of baseline and had only stopped one AED before, so ESL was added as only adjunctive treatment. Patients had on average received 0.4 prior AEDs in the mono, 1.2 in the 1+, and 2.5 in the ≥2+ group. At baseline, they were on average treated with 0.0, 1.1, and 2.2 AEDs, respectively (discrepancies between group assignment and number of AEDs at the day of baseline arise because of a conversion period of 31 days after baseline). During the study, treatment with at least 1 concomitant AED was stopped in 2.9%, 19.3%, and 34.1% of patients in groups mono, 1+, and ≥2+, and 0.0%, 14.0%, and 9.1% started treatment with at least one more concomitant AED. Levetiracetam (LEV, 59.6%), lamotrigine (LTG, 15.8%), and valproic acid (VPA, 14.0%) were the most commonly prescribed concomitant AEDs in the 1+ group. In comparison, concomitant use of LTG (47.7%), lacosamide (LCM, 30.7%), and VPA (26.1%) were most frequent in the ≥2+ group.

3.3. Dosing

The target dose of ESL was lowest in the mono group (800.0 mg/d, SD = 137.2 vs. 888.5 mg/d, SD = 271.2 in the 1+ and 881.8, SD = 258.4 in the ≥2+ group), while the last documented dose was highest here with 902.9, SD = 280.2 (vs. 870.2 mg/d, SD = 329.1 and 834.1 mg/d, SD = 347.4 in the other two groups, respectively). A median of 15 days was needed to reach the target dose in the mono and ≥2+ group vs. 9 days in the 1+ group.

3.4. Retention and seizure control

Retention rates and results for seizure control are shown in Fig. 1. After 6 months, 93.9% of patients in the mono group were still on ESL, 78.0% in the 1+, and 75.3% in the ≥2+ group.

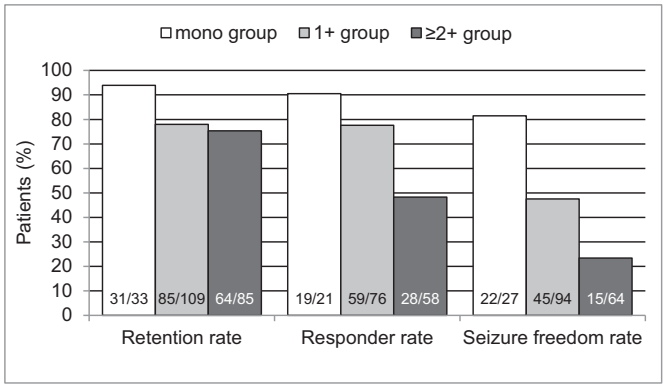

Fig. 1. Retention rate, overall responder rate, and overall seizure freedom rate at 6 months visit by subgroup. Responder rate was defined as percentage of patients with ≥50% reduction in seizure frequency compared with baseline; seizure freedom was defined as no seizure at follow-up; mono group, patients treated with ESL monotherapy; 1+ group: patients treated with 1 AED + ESL; ≥2+ group: patients treated with 2 or more AEDs + ESL; AED, antiepileptic drug; ESL, eslicarbazepine acetate.

The responder rate for all seizures was highest for the mono group, with 90.5%, followed by 77.6% for the 1+ group, and 48.3% for the ≥2+ group. For simple partial seizures, the responder rates were 80.0%, 75.0%, and 61.1%, respectively, while the percentages were 100.0%, 82.2%, and 46.6% for complex partial seizures. For secondarily generalized tonic–clonic seizures, 95.0%, 83.7%, and 80.8% of patients in the mono, 1+ and ≥2+ groups were responders, respectively.

In the mono group, 81.5% were completely seizure-free at follow-up and 47.9% in the 1+ group, approximately doubling the rate of the ≥2+ group (23.4%). For simple partial seizures, 92.9% in the mono group were seizure-free, 86.6% in the 1+, and 81.4% in the ≥2+ group. Concerning complex partial seizures, 82.8%, 74.5%, and 38.8% became seizure-free, respectively. Of the three groups, 90.0%, 79.6%, and 81.7% were seizure-free for secondarily generalized seizures. Median percent change in seizure frequency at follow-up compared with baseline for all seizures was −100.0% in the mono group, −79.5% in the 1+ group, and −45.6% in the ≥2+ group. For simple partial seizures, the percentages were −100.0%, −99.3%, and −63.3% for the three groups, and −100.0%, −93.1%, and −44.1% for complex partial seizures. For secondarily generalized tonic–clonic seizures, the median percent change in seizure frequency was −100% in all groups. For 17 patients (7.3%), follow-up duration was 90 days or less. Post hoc sensitivity analyses excluding this group of patients led to similar results for the efficacy outcome measures responder and seizure freedom rate for all seizures (differences ≤3%, data not shown).

3.5. Safety and tolerability

Adverse drug reactions occurred in 11.4% of patients in the mono, 19.3% in the +1, and 28.4% of patients in the ≥2+ group (Table 2). Only dizziness, fatigue, and hyponatremia occurred in more than 3% of all patients. Of the 8 cases with hyponatremia reported as ADR, 5 were considered serious, all within the add-on groups. The reported sodium levels were 118 mmol/l, 124 mmol/l (n = 2), 125 mmol/l (n = 2), and 128 mmol/l, with two cases without reported laboratory values. At the onset of hyponatremia, the ESL dose ranged between 400 mg/d and 1600 mg/d. The maximum approved dose in adjunctive therapy is 1200 mg/d. Five patients recovered, 3 after symptomatic treatment of hyponatremia (one of these patients also discontinued ESL treatment because of other reasons), 1 after discontinuation of ESL treatment, and 1 after inpatient admission. One serious case of hyponatremia improved after symptomatic treatment; 2 nonserious cases were ongoing at the follow-up visit.

Nine patients (7.9%) in the +1 group and 8 (9.1%) in the ≥2+ group experienced SAEs. After intervention and/or discontinuation of treatment with ESL, SAEs improved in one and reversed in 10 patients, while information for one patient is missing. Five deaths were recorded (3 in +1, 2 in ≥2+ group) because of pneumonia, death in senium, stroke, metastatic malign melanoma and suicide, of which 4 were not considered to be related to ESL therapy. The fifth death was the suicide that was considered to be possibly related to ESL therapy, although the patient's known past history of depression and substance abuse with psychoses may provide an alternative explanation. After LEV had been used concomitantly with ESL during the first 2 months of the observation period, comedication at the time of suicide consisted of LTG and citalopram. The rate of treatment discontinuation was 6.1% in the mono group, 22.0% in the 1+, and 24.7% in the ≥2+ group. For 3.0%, 11.0%, and 12.9% of the three groups, respectively, lack of tolerability was stated as the main reason for treatment discontinuation.

Table 2
Incidence of adverse events reported during the study and treatment discontinuation.

	Mono group, n (%)	1+ group, n (%)	≥2+ group, n (%)
	(n = 35)	(n = 114)	(n = 88)
Incidence of ADRs[a]	4 (11.4)	22 (19.3)	25 (28.4)
ADR[a] in ≥ 2% of patients and n ≥ 2 in either group			
Dizziness	0 (0.0)	5 (4.4)	7 (8.0)
Fatigue	0 (0.0)	2 (1.8)	6 (6.8)
Hyponatremia	1 (2.9)	4 (3.5)	3 (3.4)
Seizures[b]	0 (0.0)	3 (2.6)	4 (4.5)
Nausea	1 (2.9)	3 (2.6)	2 (2.3)
Skin reactions[c]	2 (5.7)	2 (1.8)	0 (0.0)
Somnolence	0 (0.0)	2 (1.8)	2 (2.3)
Headache	0 (0.0)	1 (0.9)	2 (2.3)
SAEs	0 (0.0)	9 (7.9)	8 (9.1)
Treatment discontinuation[d]	2 (6.1)	24 (22.0)	21 (24.7)
Main reason: lack of tolerability	1 (3.0)	12 (11.0)	11 (12.9)

ADR, adverse drug reaction; SAE, serious adverse event.
[a] Defined as adverse events considered at least possibly related to treatment by investigator, based on MedDRA preferred terms.
[b] Categorized by high-level group term *seizures including subtypes*.
[c] Categorized by system organ class *skin reactions and subcutaneous disorders*.
[d] Patients with available data: 33 in the mono, 109 in the 1+, 85 in the ≥2+ group.

3.6. Other outcome parameters/quality of life and cognition

The QoL was assessed by QOLIE-10. At baseline, the median QOLIE-10 score was 74.1 in the mono group (n = 28), 51.3 in the 1+ group (n = 105), and 53.3 in the 2+ group (n = 77). At follow-up, the scores were 78.9 (n = 31), 73.8 (n = 84), and 67.8 (n = 69), respectively. Standard values for cognitive functioning assessed by the NeuroCogFX were 85.0 (n = 53) at baseline and 88.0 (n = 29) at follow-up. Because of small numbers of patients, the three groups were not analyzed separately with regard to cognitive follow-up values.

4. Discussion

The ZEDEBAC study offers an interesting opportunity to contrast real-world outcomes with ESL observed in different patient groups. Patients were enrolled by invitation into this prospective observational trial, based on the number of baseline AEDs, which naturally resulted in three groups with distinct baseline demographics and epilepsy-related variables. The mono group was smaller than the adjunctive groups, possibly due to a shorter recruitment period and less frequent use of monotherapy in clinical practice right after monotherapy approval was granted in Europe. Therefore, group comparisons should be interpreted with caution. Patients of the mono group were older than patients of the 1+ group (54.5 years vs. 51.6 years), who were older than patients in the ≥2+ group (45.1 years), and considerably older than patients involved in the ESL phase III monotherapy and adjunctive trials, in which the mean age was approximately 38 years [18,19]. The different age structure is also reflected by the fact that 31.4% and 29.2% of patients in the mono and the 1+ group were ≥65 years old, vs. only 13.6% of patients in the ≥2+ group. As at the same time, epilepsy duration was shortest in the mono, followed by the 1+ group, in which the majority of patients received 1 AED at baseline and had only received one prior AED or none, it can be concluded that the mono and the 1+ groups consist of patients who developed their epilepsies later in life, to larger parts. This assumption is also supported by the composition of etiologies in these groups, which were mainly tumor-related or vascular, the two most common causes of epilepsy in elderly patients [28].

The proportion of elderly patients in this study was large with nearly one quarter of the total population and most pronounced in the mono and 1+ group. This is not surprising as the incidence of epilepsy increases in people of higher age [28] and such newly diagnosed late-onset epilepsies are primarily treated with AED monotherapy and tend to be more easily controlled by AEDs than epilepsies in younger adults [29]. Furthermore, elderly patients are at a higher risk for AEs (due to interactions between AEDs and treatments for comorbidities and age-related physiological changes), so the tolerability profile of an AED

becomes more important in the treatment decision. Eslicarbazepine acetate has been shown to be well-tolerated in elderly patients in previous studies [30,31], which may offer a possible explanation for the large amount of elderly patients in this study.

For the ≥2+ group, the group determinant "AED polytherapy at baseline", the duration of epilepsy with 18.7 years, the highest number of previous AEDs, and the highest incidence of hippocampal sclerosis compared with the other groups indicate that this group, in the majority, consists of patients with more difficult-to-treat epilepsies. Interestingly, besides LEV, which was the preferred combination partner for both add-on groups with >50% concomitant use, SCBs like LTG (>40%) and lacosamide (>30%) were commonly coadministered with ESL in the ≥2+ group, which would not be in line with a "rational polytherapy" approach in the truest sense. While combinations of SCBs have been described as being associated with an increased risk of AEs and therapy failure [13,32], the fact that the use of ESL with other SCBs has been described as frequent (53.6% at baseline) in a large pan-European observational study as well, along with a still favorable seizure outcome [20], these data may add to the perception that ESL can be a useful combination partner in polytherapy in clinical practice with concomitant SCBs. Still, ESL titration took longer in the ≥2+ group (median 15 days) than in the 1+ group (9 days), and doses were lowest in the ≥2+ group, probably reflective of a more careful dose finding approach with higher drug loads and presence of concomitant SCBs at baseline.

The incidence of ADRs in the ≥2+ group was highest with 28.4%, followed by 19.3% in the 1+, and 11.4% in the mono group, whereas treatment discontinuations due to AEs did not substantially differ between groups with 3.0% in the mono group, 11.0% in the 1+ group, and 12.9% in the ≥2+ group. The difference in incidence of ADRs is likely attributable to different levels of drug loads that have been shown in another study to have an impact on tolerability [15]. Furthermore, the relatively low incidence of ADRs and treatment discontinuations in the groups with higher mean age may offer an explanation for the choice of ESL for elderly patients with late-onset epilepsies who are more sensitive to AEs [5,6,33]. The QOLIE-10 scores at baseline were slightly lower in the adjunctive groups but had slightly improved in all groups at follow-up. This finding is in line with the described QoL profile for ESL in the longer term [34]. Results regarding cognitive functioning at baseline for all patients were slightly below average as compared with healthy controls but remained stable throughout the study, although based on a low number of observations.

In terms of treatment efficacy, e.g., seizure freedom with 81.5% in the mono vs. 23% in the ≥2+ vs. 48.2% in the 1+ group, the groups seem to differ more obviously than for the other outcome measure described, likely attributable to different levels of treatment refractoriness indicated by number of prior AEDs. This result is in line with Schiller & Najjar, who found that AED treatment history was predictive for therapy response to each consecutive AED [35]. The retention rates of ESL at 6 months in the mono and 1+ group (93.9% and 78.0%) resemble the retention rates of 98.0% and 82.2% after 6 months described in two other observational studies, in which ESL was administered as monotherapy [36] or as only add-on to a current monotherapy, respectively [37].

The ZEDEBAC study investigated ESL retention after 6 months. This time period may be relatively short for assessing longer term retention, so retention rates should be interpreted with caution. However, a follow-up of six months was applied in other studies investigating retention as well [38–40]. Additionally, retention rates in studies reporting data from the 6- and 12-month time points were relatively stable over time, with a similar relative decline from 6 to 12 months of 8–12% [41–43], so the 6-month data had a predictive value for 12 months retention. Retention rates are similar to those reported in other studies on ESL and different more recent AEDs, ranging around 80% after 6 months [41–43]. While rates of discontinuation of up to 23.9% in ≥2+ group seem quite high, this is in line with discontinuation rates reported for other modern AEDs [38,41,44]. Retention rates are determined by a variety of factors including study design and baseline characteristics such as treatment refractoriness, age, and etiology, which need to be considered when comparing different studies. Six months retention is favorable across all groups including the ≥2 group (retention rate here 75.3%), and ESL seems to be well tolerated also in those groups of expected higher sensitivities to adverse effects like elderly patients [6] in the mono group and patients with multiple SCBs and higher drug loads in the ≥2+ group [5,16]. Therefore, the results of this study may strengthen the assumption that long-term retention of a drug is primarily determined by its tolerability profile [45].

5. Conclusion

We conclude that the prospective noninterventional ZEDEBAC study provides valuable insights into the use and treatment outcomes in clinical practice in Germany with ESL in adult patients with partial-onset seizures. Results regarding retention, tolerability, and efficacy are consistent with previous observational trial data and indicate that ESL may be a suitable option for different patient populations including the elderly and therapeutic scenarios, from anticonvulsant monotherapy to more complex therapeutic situations with concomitant SCBs.

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Declaration of competing interest

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