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Eslicarbazepine acetate in epilepsy patients with psychiatric comorbidities and intellectual disability: Clinical practice findings from the Euro-Esli study

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ABSTRACT

Psychiatric and intellectual comorbidities are common in patients with epilepsy. However, data on the use of antiepileptic drugs in these patients are still lacking. This study assessed the real-world effectiveness and safety/tolerability of eslicarbazepine acetate (ESL) in patients with intellectual disability and psychiatric comorbidities, including a separate analysis specifically in those with depression, using data from the Euro-Esli study. Effectiveness measures included responder and seizure freedom rates. Safety and tolerability were assessed by evaluating adverse events (AEs) and ESL discontinuation due to AEs, respectively. Of the 2058 patients initially included in the Euro-Esli study, 952 patients had intellectual disability data available, 1138 had psychiatric comorbidity data available and 1134 had depression data available. Of those who had intellectual or psychiatric comorbidity data available, 11.3% (108/952) suffered from intellectual disability, 24.9% (283/1138) had a psychiatric disorder, including depression, and 12.4% (141/1134) specifically had depression. Responder and seizure freedom rates were generally comparable between patients with psychiatric comorbidity and those without, and patients with depression and those without. However, responder and seizure freedom rates were significantly lower in patients with intellectual disability compared with those without. Overall, patients with psychiatric and intellectual comorbidities experienced more AEs and AEs leading to ESL discontinuation than patients without these comorbidities. The incidence of psychiatric AEs was not significantly different for patients with psychiatric comorbidities or depression than those without, and the incidence of cognitive AEs was not significantly different for patients with intellectual disability than those without. These findings suggest that ESL is effective in patients with psychiatric and intellectual comorbidities and that its use in these patients is unlikely to exacerbate existing psychiatric or cognitive disturbances.

1. Introduction

Psychiatric disorders and intellectual disability are frequently encountered in patients with epilepsy [1–3]. In fact, the prevalence of psychiatric comorbidity is two-fold higher in patients with epilepsy than in the general population [2]. Affective disorders are the most common culprit, with depression accounting for 30% of all affective conditions in these patients [4,5]. The etiology of depression and other psychiatric comorbidities in patients with epilepsy is multifaceted with clear psychosocial predisposition, but iatrogenic causes are often implicated [4,6,7]. Furthermore, numerous studies have shown that psychiatric comorbidities, especially depression, negatively affect the quality of life (QoL) of patients with epilepsy and result in additional healthcare costs and loss of productivity due to absenteeism [8,9].

Intellectual disability is another common comorbidity in epilepsy patients, affecting up to a quarter of patients [10]. The underlying

Abbreviations: AE, adverse event; AED, antiepileptic drug; ESL, eslicarbazepine acetate; ID, intellectual disability; ILAE, International League Against Epilepsy; NOC, not otherwise classified; QoL, quality of life; SD, standard deviation

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etiology of epilepsy can itself be the reason for a number of cognitive and behavioral challenges, which may be aggravated by antiepileptic drug (AED) therapy [11]. The treatment of patients with intellectual disability is further complicated by the fact that such patients are more prone to psychiatric disorders [3,12–15] and more refractory to AED therapy, compared with patients without intellectual disability [15–18]. In addition, in patients with intellectual disability, epilepsy tends to be more severe and chronic, leading to increased health service utilization, morbidity and mortality, compared with epilepsy in the general population [19,20].

Medication tolerability is an important aspect of managing epilepsy treatment in patients with comorbidities. New generation AED treatments have emerged as useful alternatives to older therapies with improvement in safety and tolerability profiles, when treating these patient populations [21,22]. However, neuropsychiatric adverse events (AEs) are still problematic [23–26].

Eslicarbazepine acetate (ESL) – a once-daily AED approved for the treatment of focal-onset seizures as monotherapy or adjunctive therapy – is a potentially valuable therapy for patients suffering from psychiatric disorders or intellectual disability, since psychiatric AEs are uncommonly reported with ESL, with the exception of insomnia [27–29]. The efficacy and safety of ESL as a treatment for focal epilepsy have been established in a series of randomized controlled trials [30–36] and extension studies [37–39]. However, data on the effectiveness of ESL in patients with psychiatric or intellectual comorbidities are still lacking. This lack of information is perhaps unsurprising given that controlled trials employ strict inclusion criteria; patients are carefully recruited to minimize the effect of confounding factors that might impact efficacy and/or safety results [40].

To bridge the gap between clinical trials and real-life experience with ESL, a large clinical audit (the Euro-Esli study) was conducted, which pooled and analyzed data from European clinical practice studies [41]. Euro-Esli included 2058 patients, representing the largest cohort of patients treated with ESL in clinical practice to be reported to date. The size of the patient cohort has allowed meaningful subgroup analyses to be conducted.

The aim of this study was to assess ESL in patients with focal epilepsy, from Euro-Esli, presenting with intellectual or psychiatric comorbidities (including depression), and to establish whether the efficacy and tolerability profiles reported for ESL in clinical trials are reflected in the clinical practice setting when treating these patients. Since depression is a common psychiatric presentation amongst epilepsy patients, a separate analysis was also conducted in this specific population.

2. Methods

2.1. Study design

The Euro-Esli study was an exploratory, retrospective, pooled analysis of data from 14 European clinical real-world practice studies that assessed the effectiveness, safety and tolerability of ESL as an adjunctive treatment for focal seizures. Details of the specific inclusion/exclusion criteria used in the individual studies have been previously reported [41–54]. Overall, these studies included few inclusion/exclusion criteria, to mirror the diversity of patients encountered in clinical practice.

The current subanalyses included patients treated with ESL for whom intellectual disability, psychiatric comorbidity (including depression) and/or depression data were available. Diagnostic criteria for intellectual disability, psychiatric comorbidity and depression were defined by the participating physicians according to information extracted from medical records. Effectiveness was assessed after 3, 6 and 12 months of ESL treatment and at final follow-up. Safety and tolerability were assessed throughout ESL treatment.

2.2. Study assessments

2.2.1. Effectiveness

Effectiveness measures included responder, seizure freedom and retention rates. Response to ESL treatment was defined as ≥50% seizure frequency reduction from baseline (prior to ESL initiation) and seizure freedom was defined as no reported seizures since at least the prior visit (either 3 or 6 months).

2.2.2. Safety and tolerability

Safety was assessed by evaluation of AEs and tolerability was assessed by analysing treatment discontinuation due to AEs. AEs were classified using the Medical Dictionary for Regulatory Activities version 16.0 [55]. Certain AEs of special interest were also assessed, which were psychiatric disorders (as a system organ class), cognitive AEs (defined as 'Disturbance in attention/concentration', 'Memory problems', 'Confusion', 'Cognitive disturbance', 'Sedation', 'Encephalopathy' and 'Bradypsychia'), and hyponatremia.

2.2.3. Additional assessments

These included evaluation of information relating to ESL dosing, time to ESL discontinuation and changes to concomitant AED(s) after initiation of ESL treatment.

2.3. Statistical analyses

Details of the statistical methodology employed in Euro-Esli have been previously published [41]. The efficacy population included all patients who initiated ESL treatment and had at least one efficacy assessment. The safety population was defined as all patients who initiated ESL treatment. Effectiveness, safety and tolerability data were not available for all patients at every timepoint; therefore, the denominator used for all frequency assessments was the total number of patients for whom the data in question were available. Patients who withdrew from ESL treatment were not excluded from the analysis; the 'last visit' timepoint was created in order to capture the patients' last recorded observation for each assessment.

In these subanalyses, differences in baseline characteristics were analyzed using the Chi-squared test, Student's *t*-test or Mann–Whitney *U* test, as appropriate. ESL dose variation between patients with versus without comorbidities at various timepoints was assessed using the Mann–Whitney U test. Variation between the initial and final number of concomitant AEDs in each patient subgroup was assessed using the Wilcoxon signed-rank test, while the difference between concomitant AEDs between patients with versus without comorbidities at baseline and last visit was assessed using the Mann–Whitney *U* test. Treatment response and safety and tolerability assessments were summarized descriptively and studied as a function of the different subpopulations using the Chi-squared test. Time to ESL discontinuation was assessed using the Kaplan–Meier method. Differences in ESL treatment retention between patients with versus without comorbidities was performed using the Log Rank test.

The Statistical Package for the Social Sciences version 19.0 was used for all analyses. The significance level was set at 5%.

3. Results

Of the 2058 patients initially included in the Euro-Esli study [41], 952 patients had intellectual disability data available, 1138 had psychiatric comorbidity data available and 1134 had depression data available. Of those who had intellectual or psychiatric comorbidity data available, 11.3% (108/952) suffered from intellectual disability, 24.9% (283/1138) had a psychiatric disorder, including depression, and 12.4% (141/1134) specifically had depression. The range of disorders present in the psychiatric comorbidity subgroup are detailed in Table 1. Depression affected almost half of patients who reported psychiatric

Table 1
Breakdown of the types of disorders present in the psychiatric comorbidities subgroup (283 patients).

Disorder[a]	n (%)
Organic, including symptomatic, mental disorders	
Dementia	1 (0.4)
Mental and behavioral disorders due to psychoactive substance abuse	
Substance abuse	21 (7.4)
Schizophrenia, schizotypal and delusional disorders	
Unspecified psychosis	15 (5.3)
Schizophrenia NOC	6 (2.1)
Mood (affective) disorders	
Depression	141 (49.8)
Mood disorder	26 (9.2)
Bipolar affective disorder	3 (1.1)
Cyclothymia	1 (0.4)
Manic episode	1 (0.4)
Neurotic, stress-related and somatoform disorders	
Anxiety	59 (20.8)
Panic disorder	7 (2.5)
Dissociative (conversion) disorders	6 (2.1)
Neurotic disorders	2 (0.7)
Adjustment disorder	1 (0.4)
Multiple personality	1 (0.4)
Neurasthenia	1 (0.4)
Post-traumatic stress disorder	1 (0.4)
Behavioral syndromes associated with physiological disturbances and physical factors	
Anorexia nervosa	2 (0.7)
Insomnia	3 (1.1)
Disorders of adult personality and behavior	
Personality disorder	11 (3.9)
Conduct disorders	10 (3.5)
Borderline personality disorder	1 (0.4)
Disorders of psychological development	
Asperger syndrome	2 (0.7)
Behavioral and emotional disorders with onset usually occurring in childhood and adolescence	
Attention-deficit hyperactivity disorder	11 (3.9)
Unspecified mental disorder	
Psychological disorders NOC	30 (10.6)

NOC, not otherwise classified.
[a] International Statistical Classification of Diseases and Related Health Problems, 10th Revision.

comorbidities while anxiety affected a fifth of these patients (Table 1).

3.1. Study population

The baseline characteristics of the full Euro-Esli study population have been described previously [41]. In brief, the mean age of patients was 44.0 years; 52.1% of patients were male; the mean age at onset of epilepsy was 23.3 years; and the mean duration of epilepsy was 20.9 years. The baseline characteristics of patients with and without psychiatric comorbidity or intellectual disability included in these subanalyses are presented in Table 2.

3.1.1. Intellectual disability

Patients with intellectual disability were younger than those without ($p < .001$), and the mean age of epilepsy onset was recorded at an earlier age in patients with intellectual disability compared with those without ($p < .001$) (Table 2). In addition, the mean duration of the disease was longer in patients with intellectual disability than those without ($p = .009$). The use of previous AEDs was significantly higher in the group of patients with intellectual disability compared to those without ($p < .001$). Overall seizure activity was also higher in the group of patients with intellectual disability compared with those without ($p < .001$).

3.1.2. Psychiatric comorbidity

A higher proportion of patients with psychiatric comorbidities were female compared to those without psychiatric comorbidities ($p = .003$) (Table 2). Mean monthly seizure frequency was similar between the two groups of patients ($p = .352$), while baseline numbers of previous AEDs were higher in the psychiatric comorbidity group compared to the no psychiatric comorbidity group ($p = .041$).

3.1.3. Depression

Patients who suffered from depression were slightly older than those who did not ($p = .032$) (Table 2). The proportion of females was also higher in the group of patients with depression compared to those without ($p = .039$). The use of previous AEDs was higher in the group of patients with depression compared with those without ($p = .020$), although at baseline, the number of concomitant AEDs was similar between the two groups ($p = .283$) (Table 3).

3.2. ESL treatment

The most common reason for ESL initiation in the different patient groups included in these subanalyses was lack of effectiveness of previous treatment (Table 3).

3.2.1. Intellectual disability

At baseline, the median ESL dose at initiation was 400 mg/day in both patients with intellectual disability and those without (Table 3). At the last visit, the ESL dose was higher in patients with intellectual disability compared with those without ($p = .044$; Mann–Whitney U test). In patients with intellectual disability, the number of concomitant AEDs did not differ significantly throughout the study ($p = .317$; Wilcoxon signed-rank test). However, the use of concomitant AEDs reduced significantly in patients without intellectual disability ($p < .001$; Wilcoxon signed-rank test). At last follow-up, the number of concomitant AEDs was statistically higher in the group of patients with intellectual disability compared with those without ($p < .001$; Mann–Whitney U test).

3.2.2. Psychiatric comorbidity

ESL dosing was similar between patients with and without psychiatric comorbidity at initiation (baseline) and last visit (Table 3). There was a significant reduction in the number of concomitant AEDs used from baseline to the last visit in patients with psychiatric comorbidity ($p < .001$; Wilcoxon signed-rank test) and those without ($p < .001$; Wilcoxon signed-rank test). At last follow-up, there was no statistically significant difference in the number of concomitant AEDs between the two groups ($p = .09$; Mann–Whitney U test).

3.2.3. Depression

No statistical differences in dosing were detected between the two groups of patients at initiation (baseline) and last follow-up (Table 3). There was a significant reduction in the number of concomitant AEDs used from baseline to the last visit in patients with depression ($p < .001$; Wilcoxon signed-rank test) and those without ($p < .001$; Wilcoxon signed-rank test).

3.3. Effectiveness

3.3.1. Intellectual disability

At all timepoints, responder and seizure freedom rates were significantly lower in patients with intellectual disability compared with those without (Fig. 1). At 12 months, 60.3% (35/58) of patients in the intellectual disability group had responded to ESL treatment compared with 76.6% (222/290) of patients in the no intellectual disability group ($p = .010$, Chi-squared test). The rate of seizure freedom after 12 months of ESL treatment was 22.4% (13/58) in patients with intellectual disability compared with 43.1% (125/290) in patients

Table 2
Patient demographics and baseline characteristics in patients with intellectual disability or psychiatric comorbidity and those without.

Baseline demographics	Intellectual disability		Psychiatric comorbidity		Depression	
	Yes	No	Yes	No	Yes	No
Age						
N[a]	108	844	283	855	141	993
Mean (SD), year	38.2 (13.2)	44.7 (14.6)	46.5 (15.6)	45.0 (15.9)	47.8 (14.3)	45.0 (16.1)
Median (range), year	36.0 (16.0–77.0)	43.0 (17.0–85.0)	47.0 (18.0–87.0)	43.0 (17.0–87.0)	48.0 (19.0–83.0)	43.0 (17.0–87.0)
p-value	< 0.001[c]		0.175[c]		0.032[c]	
Sex						
N[a]	107	844	283	854	141	992
Male, *n* (%)	57 (53.3)	449 (53.2)	132 (46.6)	486 (56.9)	65 (46.1)	549 (55.3)
Female, *n* (%)	50 (46.7)	395 (46.8)	151 (53.4)	368 (43.1)	76 (53.9)	443 (44.7)
p-value	0.989[b]		0.003[b]		0.039[b]	
Epilepsy-related characteristics						
Age at onset of epilepsy						
N[a]	98	801	269	816	135	946
Mean (SD), year	10.2 (14.1)	20.8 (17.1)	27.0 (20.5)	24.5 (20.3)	25.5 (20.2)	25.0 (20.4)
Median (range), year	4.0 (0.0–61.0)	17.0 (0.0–82.0)	23.0 (0.0–83.0)	20.0 (0.0–87.0)	22.0 (0.0–81.0)	20.0 (0.0–87.0)
p-value	< 0.001[d]		0.049[d]		0.696[d]	
Duration of epilepsy						
N[a]	98	801	269	816	135	946
Mean (SD), years	27.6 (15.0)	24.2 (17.3)	19.5 (16.6)	21.0 (17.7)	22.4 (18.0)	20.4 (17.4)
Median (range), years	28.0 (0.0–73.0)	22.0 (0.0–81.8)	15.5 (0.0–73.0)	17.0 (0.0–81.8)	20.0 (0.0–73.0)	16.5 (0.0–81.8)
p-value	0.009[d]		0.325[d]		0.210[d]	
Etiology (ILAE 2010 classification)						
N[a]	104	596	252	634	118	764
Structural-metabolic, *n* (%)	41 (39.4)	305 (51.2)	125 (49.6)	345 (54.4)	53 (44.9)	414 (54.2)
Genetic, *n* (%)	4 (3.8)	13 (2.2)	4 (1.6)	13 (2.1)	1 (0.8)	16 (2.1)
Unknown, *n* (%)	59 (56.7)	278 (46.6)	123 (48.8)	276 (43.5)	64 (54.2)	334 (43.7)
p-value	0.069[b]		0.349[b]		0.082[b]	
Baseline seizure type						
Any seizure						
N[a]	107	842	282	853	141	990
Yes, *n* (%)	103 (96.3)	790 (93.8)	252 (89.4)	807 (94.6)	126 (89.4)	929 (93.8)
p-value	0.314[b]		0.002[b]		0.047[b]	
Simple partial seizures						
N[a]	106	841	277	840	138	975
Yes, *n* (%)	13 (12.3)	262 (31.2)	71 (25.6)	263 (31.3)	41 (29.7)	292 (29.9)
p-value	< 0.001[b]		0.073[b]		0.954[b]	
Complex partial seizures						
N[a]	106	841	277	840	138	975
Yes, *n* (%)	63 (59.4)	531 (63.1)	154 (55.6)	500 (59.5)	84 (60.9)	567 (58.2)
p-value	0.457[b]		0.250[b]		0.545[b]	
Secondarily generalized seizures						
N[a]	106	841	277	840	138	975
Yes, *n* (%)	79 (74.5)	416 (49.5)	153 (55.2)	412 (49.0)	72 (52.2)	490 (50.3)
p-value	< 0.001[b]		0.074[b]		0.673[b]	
Monthly seizure frequency						
Any seizure						
N[a]	103	790	252	807	126	929
Mean (SD)	26.8 (65.4)	15.5 (66.7)	10.8 (30.7)	14.2 (67.9)	12.8 (35.7)	13.5 (64.0)
Median (range)	6.0 (0.3–495.0)	3.0 (0.2–1230.0)	2.7 (0.1–300.0)	2.3 (0.1–1230.0)	3.0 (0.1–300.0)	2.3 (0.1–1230.0)
p-value	< 0.001[d]		0.352[d]		0.066[d]	
Simple partial seizures						
N[a]	8	200	49	221	28	241
Mean (SD)	9.4 (16.6)	18.4 (80.8)	10.6 (24.3)	15.6 (76.5)	12.4 (28.2)	15.0 (73.4)
Median (range)	3.2 (0.7–50.0)	3.2 (0.3–900.0)	3.3 (0.3–150.0)	2.0 (0.3–900.0)	2.0 (0.3–150.0)	4.0 (0.3–900.0)
p-value	0.748[d]		0.057[d]		0.023[d]	
Complex partial seizures						
N[a]	30	427	119	428	68	476
Mean (SD)	17.9 (38.5)	8.2 (24.5)	8.0 (26.3)	6.5 (22.6)	6.5 (17.1)	6.9 (24.3)
Median (range)	5.0 (0.3–200.0)	2.8 (0.2–300.0)	2.5 (0.3–240.0)	2.0 (0.2–300.0)	2.0 (0.3–125.0)	2.7 (0.2–300.0)
p-value	0.011[d]		0.057[d]		0.379[d]	
Secondarily generalized seizures						
N[a]	45	318	118	342	56	401
Mean (SD)	6.7 (10.6)	2.4 (5.6)	2.7 (6.2)	2.1 (5.1)	2.9 (6.9)	2.2 (5.2)
Median (range)	3.0 (0.2–51.0)	0.9 (0.1–50.0)	1.0 (0.2–45.0)	0.7 (0.1–50.0)	1.0 (0.2–45.0)	0.7 (0.1–50.0)
p-value	< 0.001[d]		0.064[d]		0.024[d]	

(*continued on next page*)

Table 2 (*continued*)

Baseline demographics	Intellectual disability		Psychiatric comorbidity		Depression	
	Yes	No	Yes	No	Yes	No
AED treatment						
Total number of previous AEDs[e]						
N[a]	108	838	283	853	141	991
Mean (SD)	5.3 (4.1)	3.0 (3.0)	2.6 (3.1)	2.4 (3.1)	2.8 (3.1)	2.4 (3.1)
Median (range)	4.0 (0.0–15.0)	2.0 (0.0–15.0)	2.0 (0.0–15.0)	1.0 (0.0–15.0)	2.0 (0.0–13.0)	1.0 (0.0–15.0)
p-value	< 0.001[d]		0.041[d]		0.020[d]	

AED, antiepileptic drug; ILAE, International League Against Epilepsy; SD, standard deviation.
[a] *N* refers to the total number of patients for whom data in question were available.
[b] Chi-Squared test.
[c] Student's *t*-test.
[d] Mann–Whitney *U* test.
[e] Excluding concomitant AEDs.

Table 3
ESL dosing, use of concomitant AEDs and reasons for ESL initiation or discontinuation at baseline and last visit.

	Intellectual disability		Psychiatric comorbidity		Depression	
	Yes	No	Yes	No	Yes	No
At initiation (baseline)						
ESL dose						
N[a]	7	338	110	486	52	544
Mean (SD), mg/day	457.1 (151.2)	436.8 (170.7)	493.6 (202.9)	493.3 (235.2)	490.4 (171.8)	493.7 (234.3)
Median (range), mg/day	400 (400–800)	400 (150–1600)	400 (300–1600)	400 (150–1600)	400 (300–800)	400 (150–1600)
p-value[b]	0.527		0.434		0.515	
Total number of concomitant AEDs						
N[a]	108	842	283	853	141	991
Mean (SD)	2.3 (1.2)	1.7 (1.0)	1.6 (1.0)	1.6 (1.0)	1.6 (1.0)	1.6 (1.0)
Median (range)	2.0 (0.0–5.0)	1.0 (0.0–6.0)	1.0 (0.0–5.0)	1.0 (0.0–6)	1.0 (0.0–4.0)	1.0 (0.0–6.0)
p-value[b]	< 0.001		0.090		0.283	
Reasons for ESL initiation						
N[a]	23	444	160	557	77	640
Lack of effectiveness, *n* (%)	17 (73.9)	337 (75.9)	101 (63.1)	409 (73.4)	56 (72.7)	454 (70.9)
Poor tolerability, *n* (%)	3 (13.0)	43 (9.7)	38 (23.8)	81 (14.5)	9 (11.7)	110 (17.2)
Both, *n* (%)	0	45 (10.1)	12 (7.5)	34 (6.1)	8 (10.4)	38 (5.9)
Other, *n* (%)	3 (13.0)	19 (4.3)	9 (5.6)	33 (5.9)	4 (5.2)	38 (5.9)
At last visit						
ESL dose						
N[a]	107	834	282	845	140	983
Mean (SD), mg/day	1050.5 (358.3)	981 (355.1)	982.6 (328.5)	948.0 (324.5)	985.0 (358.8)	952.9 (321.1)
Median (range), mg/day	1200 (400–2400)	800 (200–2800)	800 (400–2400)	800 (200–2800)	800 (400–2400)	800 (200–2800)
p-value[b]	0.044		0.077		0.281	
Total number of concomitant AEDs						
N[a]	54	505	170	640	78	732
Mean (SD)	2.6 (1.4)	1.5 (1.0)	1.3 (1.1)	1.3 (1.1)	1.4 (1.2)	1.3 (1.1)
Median (range)	2.5 (0.0–5.0)	1.0 (0.0–6.0)	1.0 (0.0–4.0)	1.0 (0.0–6.0)	1.0 (0.0–4.0)	1.0 (0.0–6.0)
p-value[b]	< 0.001		0.566		0.266	
Reasons for ESL discontinuation						
N[a]	103	827	276	840	138	974
Lack of effectiveness, *n* (%)	15 (14.6)	49 (5.9)	18 (6.5)	40 (4.8)	11 (8.0)	46 (4.7)
Poor tolerability, *n* (%)	11 (10.7)	91 (11.0)	37 (13.4)	69 (8.2)	20 (14.5)	85 (8.7)
Both, *n* (%)	11 (10.7)	26 (3.1)	8 (2.9)	25 (3.0)	4 (2.9)	29 (3.0)
Other, *n* (%)	9 (8.7)	56 (6.8)	25 (9.1)	44 (5.2)	13 (9.4)	56 (5.7)

AED, antiepileptic drug; ESL, eslicarbazepine acetate; SD, standard deviation.
[a] *N* refers to the total number of patients for whom data in question were available.
[b] Mann–Whitney U test.

without ($p = .003$; Chi-squared test).

At 12 months of follow-up, retention on ESL treatment was 67.6% (69/102) in patients with intellectual disability and 78.7% (657/835) in patients without. During the same period, the mean duration of ESL treatment was 9.7 months (95% confidence interval [CI]: 9.1–10.4 months) in patients with intellectual disability and 10.1 months (95% CI: 9.9–10.4 months) in patients without intellectual disability ($p = .090$; Log Rank test).

3.3.2. Psychiatric comorbidity

At all timepoints, there were no significant differences between groups in responder and seizure freedom rates (Fig. 2). At 12 months, the responder rates were 83.1% (128/154) and 82.5% (326/395) in patients with and without psychiatric comorbidity, respectively (Fig. 2). The rate of seizure freedom after 12 months of ESL treatment was 51.3% (79/154) in patients with psychiatric disorders and 51.4% (203/395) in patients without.

At 12 months of follow-up, ESL retention rate was 75.1% (211/281)

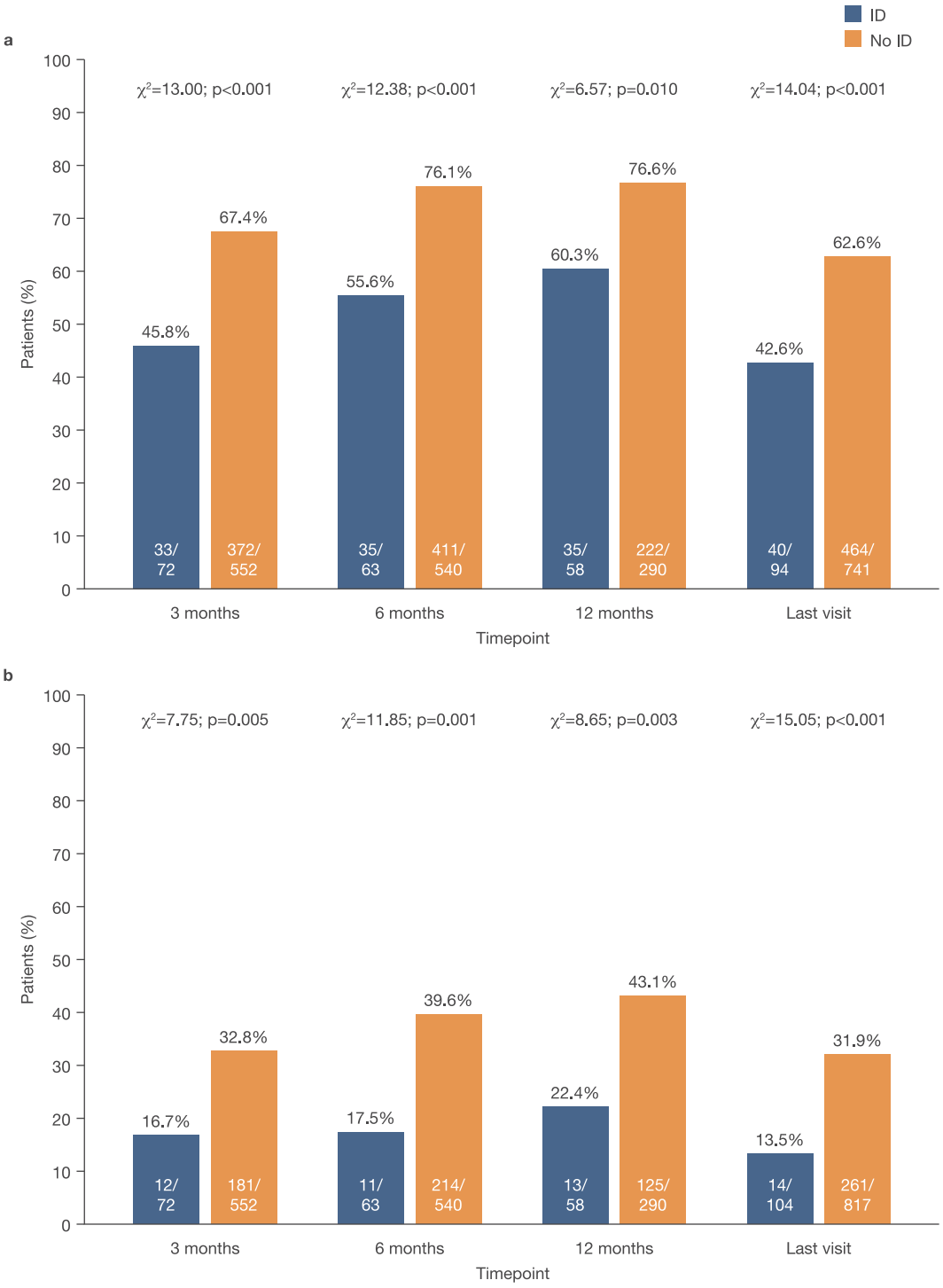

Fig. 1. Effectiveness of eslicarbazepine acetate in patients with intellectual disability and those with no intellectual disability: (a) responder rate and (b) seizure freedom rate at 3 months, 6 months, 12 months and the last visit. Response was defined as ≥50% reduction in seizure frequency from baseline. Seizure freedom was defined as no seizures since at least the prior visit. ID refers to intellectual disability.

in patients with psychiatric comorbidities and 83.2% (697/838) in patients without. The mean duration of ESL treatment during this period was 9.9 months (95% CI: 9.5–10.4 months) in patients with psychiatric comorbidities and 10.6 months (95% CI: 10.4–10.8 months) in patients without psychiatric comorbidities (p = .006; Log Rank test).

3.3.3. Depression

At all but the last visit, the responder rate in epilepsy patients suffering from depression was comparable with those who did not (Supplementary file). Although seizure freedom rates were lower in patients suffering from depression compared with those who did not, the difference was statistically significant only at the 6-month visit and last follow-up (Supplementary file). After 12 months, responder and seizure freedom rates were 81.0% (51/63) and 46.0% (29/63) in patients with depression and 82.9% (402/485) and 52.0% (252/485) in patients without depression, respectively.

Retention on ESL treatment, at 12 months of follow-up, was 71.6% (101/141) in patients with depression and 82.6% (805/974) in patients

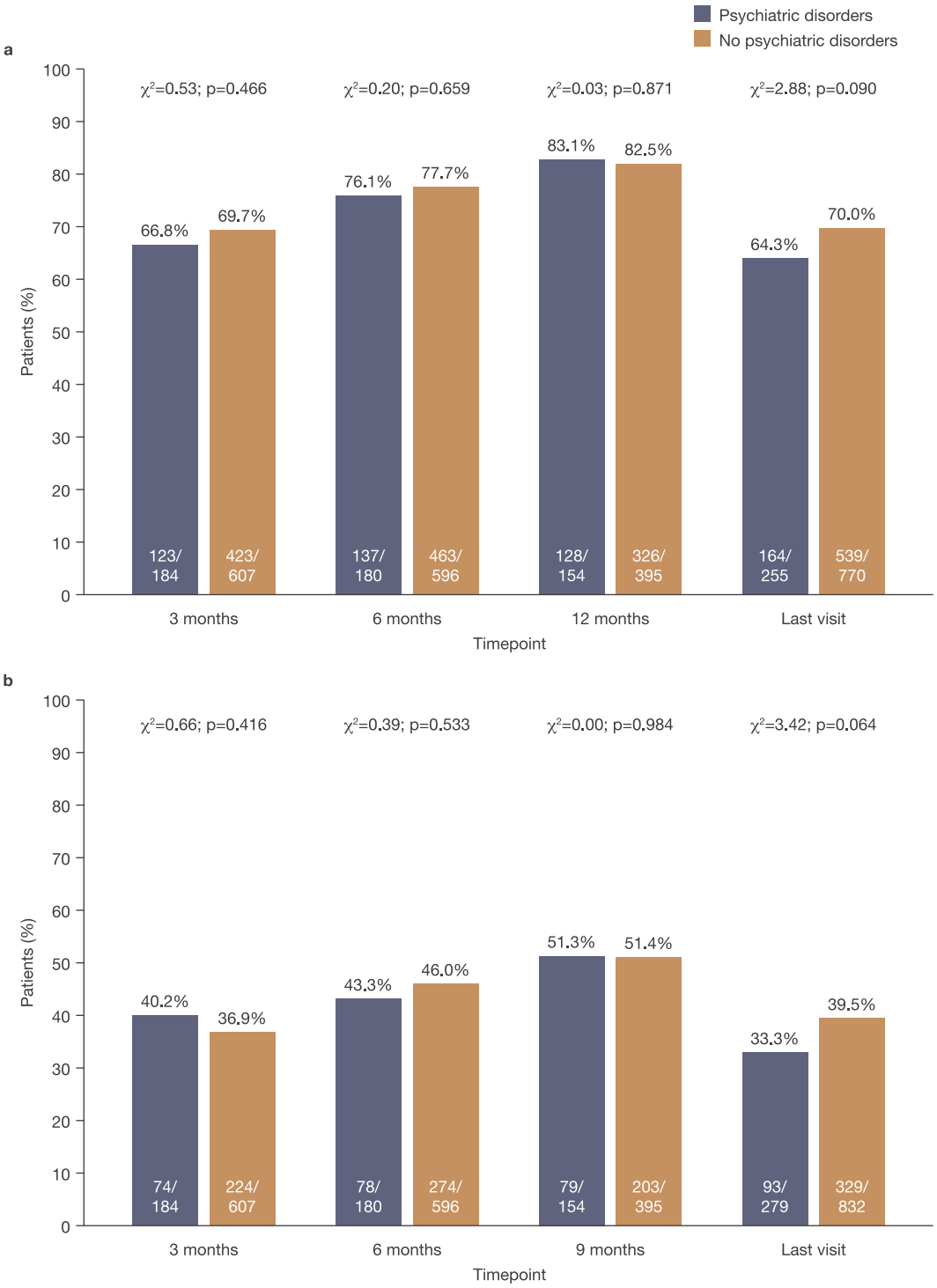

Fig. 2. Effectiveness of eslicarbazepine acetate in patients with psychiatric comorbidity and those with no psychiatric comorbidity: (a) responder rate and (b) seizure freedom rate at 3 months, 6 months, 12 months and the last visit. Response was defined as ≥50% reduction in seizure frequency from baseline. Seizure freedom was defined as no seizures since at least the prior visit.

without depression. The mean duration of ESL treatment during this period was 9.6 months (95% CI: 8.9–10.3 months) in patients with depression and 10.6 months (95% CI: 10.4–10.8 months) in those without (p = .001; Log Rank test).

3.4. Safety and tolerability

3.4.1. Intellectual disability

Patients with intellectual disability experienced more AEs than those without (45.8% [49/107] versus 32.6% [275/844]; p = .007) (Table 4). There was no statistical difference in cognitive AEs reporting in patients with intellectual disability compared with those without (4.0% [4/99] versus 3.8% [31/809]; p = .919). The incidence of psychiatric AEs, however, was higher in patients with intellectual disability than those without (6.1% [6/99] versus 1.6% [13/809]; p = .003). The incidence of AEs leading to treatment discontinuation was higher in the intellectual disability group compared with the group with no intellectual disability, although this was of marginal statistical

Table 4
Summary of AEs in patients with and without intellectual disability or psychiatric comorbidity.

	Intellectual disability		Psychiatric comorbidity		Depression	
	Yes	No	Yes	No	Yes	No
Patients with any AE						
N[a]	107	844	283	855	141	993
n (%)	49 (45.8)	275 (32.6)	122 (43.1)	261 (30.5)	60 (42.6)	322 (32.4)
p-value[b]	0.007		< 0.001		0.017	
Most frequently reported AEs (≥2% patients[c])						
N[a]	99	809	272	822	136	955
Dizziness, *n* (%)	10 (10.1)	51 (6.3)	18 (6.6)	51 (6.2)	10 (7.4)	59 (6.2)
Fatigue, *n* (%)	7 (7.1)	75 (9.3)	31 (11.4)	55 (6.7)	17 (12.5)	69 (7.2)
Somnolence, *n* (%)	6 (6.1)	34 (4.2)	22 (8.1)	34 (4.1)	11 (8.1)	45 (4.7)
Hyponatremia, *n* (%)	10 (10.1)	39 (4.8)	24 (8.8)	32 (3.9)	11 (8.1)	45 (4.7)
Instability/ataxia, *n* (%)	5 (5.1)	20 (2.5)	6 (2.2)	19 (2.3)	3 (2.2)	22 (2.3)
Diplopia/blurred vision, *n* (%)	1 (1.0)	28 (3.5)	9 (3.3)	18 (2.2)	5 (3.7)	22 (2.3)
Rash, *n* (%)	0	20 (2.5)	10 (3.7)	11 (1.3)	8 (5.9)	13 (1.4)
Nausea, *n* (%)	4 (4.0)	23 (2.8)	8 (2.9)	19 (2.3)	4 (2.9)	23 (2.4)
Disturbance in attention/concentration, *n* (%)	4 (4.0)	27 (3.3)	8 (2.9)	23 (2.8)	2 (1.5)	29 (3.0)
Headache, *n* (%)	2 (2.0)	20 (2.5)	3 (1.1)	24 (2.9)	1 (0.7)	26 (2.7)
Gait disturbance, *n* (%)	6 (6.1)	13 (1.6)	4 (1.5)	15 (1.8)	2 (1.5)	17 (1.8)
Tremor, *n* (%)	1 (1.0)	10 (1.2)	4 (1.5)	7 (0.9)	3 (2.2)	8 (0.8)
Pruritus/burning, *n* (%)	0	5 (0.6)	3 (1.1)	2 (0.2)	3 (2.2)	2 (0.2)
Behavioral disorders, *n* (%)	2 (2.0)	0	0	1 (0.1)	0	1 (0.1)
Patients with any cognitive AEs[de]						
N[a]	99	809	272	822	136	955
n (%)	4 (4.0)	31 (3.8)	10 (3.7)	32 (3.9)	3 (2.2)	39 (4.1)
p-value[b]	0.919		0.872		0.287	
Patients with any psychiatric AEs[e]						
N[a]	99	809	272	822	136	955
n (%)	6 (6.1)	13 (1.6)	10 (3.7)	15 (1.8)	6 (4.4)	19 (2.0)
p-value[b]	0.003		0.076		0.074	
Patients with AEs leading to ESL discontinuation						
N[a]	98	789	262	811	130	939
n (%)	22 (22.4)	117 (14.8)	45 (17.2)	94 (11.6)	24 (18.5)	114 (12.1)
p-value[b]	0.050		0.019		0.044	
Most frequently reported AEs leading to ESL discontinuation (> 1% patients[f])						
N[a]	91	769	252	779	126	916
Dizziness, *n* (%)	3 (3.3)	18 (2.3)	5 (2.0)	15 (1.9)	2 (1.6)	18 (2.0)
Fatigue, *n* (%)	2 (2.2)	28 (3.6)	14 (5.6)	16 (2.1)	8 (6.3)	22 (2.4)
Rash, *n* (%)	0	11 (1.4)	5 (2.0)	7 (0.9)	4 (3.2)	8 (0.9)
Somnolence, *n* (%)	2 (2.2)	18 (2.3)	7 (2.8)	12 (1.5)	4 (3.2)	15 (1.6)
Instability/ataxia, *n* (%)	2 (2.2)	9 (1.2)	1 (0.4)	9 (1.2)	0	10 (1.1)
Diplopia/blurred vision, *n* (%)	0	14 (1.8)	2 (0.8)	11 (1.4)	1 (0.8)	12 (1.6)
Nausea, *n* (%)	2 (2.2)	14 (1.8)	5 (2.0)	10 (1.3)	2 (1.6)	13 (1.4)
Disturbance in attention/concentration, *n* (%)	3 (3.3)	16 (2.1)	4 (1.6)	15 (1.9)	1 (0.8)	18 (2.0)
Hyponatremia, *n* (%)	3 (3.3)	12 (1.6)	8 (3.2)	8 (1.0)	4 (3.2)	12 (1.3)
Headache, *n* (%)	1 (1.0)	11 (1.4)	1 (0.4)	11 (1.4)	1 (0.8)	11 (1.2)
Gait disturbance, *n* (%)	4 (4.4)	6 (0.8)	0	10 (1.3)	0	10 (1.1)
Tremor, *n* (%)	1 (1.0)	2 (0.3)	2 (0.8)	1 (0.1)	2 (1.6)	1 (0.1)

AE, adverse event; ESL, eslicarbazepine acetate.
[a] *N* refers to the total number of patients for whom data in question were available.
[b] Chi-squared test.
[c] AEs reported by ≥2% of patients in any of the patient subgroups.
[d] Defined as 'Disturbance in attention/concentration', 'Memory problems', 'Confusion', 'Cognitive disturbance', 'Sedation', 'Encephalopathy' and 'Bradypsychia'.
[e] Psychiatric disorders system organ class.
[f] AEs leading to ESL discontinuation in > 1% of patients in any of the patient subgroups.

significance (22.4% [22/98] versus 14.8% [117/789]; $p = .050$).

3.4.2. Psychiatric comorbidity

The incidence of AEs was higher in patients with psychiatric comorbidity compared with those without (43.1% [122/283] versus 30.5% [261/855]; $p < .001$) (Table 4). Psychiatric AEs were reported by 3.7% (10/272) and 1.8% (15/822) of patients with and without psychiatric comorbidity, respectively ($p = .076$). The incidence of cognitive AEs was 3.7% (10/272) in patients with psychiatric comorbidities and 3.9% (32/822) in patients without psychiatric comorbidities ($p = .872$). The proportion of patients who discontinued treatment due to AEs was higher in those who suffered from psychiatric disorders than those who did not (17.2% [45/262] versus 11.6% [94/811]; $p = .019$).

3.4.3. Depression

The occurrence of AEs was higher in epilepsy patients who suffered from depression compared with those who did not (42.6% [60/141] versus 32.4% [322/993]; $p = .017$) (Table 4). Psychiatric AEs were reported by a higher percentage of patients with depression compared to those without (4.4% [6/136] versus 2.0% [19/955]); however, the difference was not statistically significant ($p = .074$). Similarly, no statistical difference was observed between the incidence of cognitive AEs in patients with depression compared with those without (2.2% [3/136] versus 4.1% [39/955]; $p = .287$).The use of selective serotonin reuptake inhibitors (SSRIs) and serotonin–norepinephrine reuptake inhibitors (SNRIs) was known in 27 patients with depression: 16 (59.3%) were treated with SSRIs and 4 (14.8%) were taking SNRIs; hyponatremia was not reported in any of these patients. A further 11 patients

with depression reported hyponatremia as an AE; antidepressant medication use is unknown in these patients. A higher percentage of patients from the depression group discontinued treatment due to AEs compared with those in the group with no depression (18.5% [24/130] versus 12.1% [114/939]; $p = .044$).

4. Discussion

The results of these subanalyses demonstrate that ESL is effective and generally well tolerated in patients with intellectual and psychiatric comorbidities. After 12 months of follow-up, almost two thirds of patients with intellectual disability responded to ESL treatment, and approximately a quarter achieved seizure freedom. In the groups of patients with psychiatric comorbidities and those specifically with depression, over 80% responded to ESL treatment and approximately half achieved seizure freedom during the same period.

Responder and seizure freedom rates were significantly lower in patients with intellectual disability than in those without, at all timepoints, possibly reflecting a higher degree of treatment refractoriness in the former group. At baseline, patients with intellectual disability used a higher number of previous and concomitant AEDs than patients without intellectual disability. While the number of concomitant AEDs reduced significantly from baseline to last follow-up following ESL treatment in patients without intellectual disability, there was no significant change in those patients with intellectual disability. It should also be noted that although baseline ESL dose was similar in the groups of patients with and without intellectual disability, at last follow-up, patients with intellectual disability received a higher ESL dose compared with patients without. These results are consistent with previous studies indicating that patients with intellectual disability are more refractory to AED treatment than those without [16,17,56].

The effectiveness of ESL in patients with psychiatric comorbidities was similar to those without at all timepoints. Similarly, response to ESL treatment was generally comparable in patients who specifically had depression compared with those who did not. By contrast, responder and seizure freedom rates were significantly lower in patients with depression compared with those without at the last visit. Responder and seizure freedom rates were also somewhat lower in patients with psychiatric comorbidities compared with those without at the last visit, although the differences were not statistically significant. These findings might have been affected by the lack of homogeneity between groups in terms of follow-up duration at the last visit assessment (since the last visit could have been at 3, 6, 12 months or later). Effectiveness assessments at the defined timepoints (3, 6 and 12 months) were more homogenous in terms of follow-up duration and therefore likely to be more reliable in terms of measured outcomes. Nevertheless, seizure freedom rates were somewhat lower in patients with depression compared with those without throughout follow-up, the difference also reaching statistical significance at 6 months.

These detected differences in responder and seizure freedom rates in patients with depression compared with those without, albeit minor, might be clinically significant, since the presence of depression can itself be a risk factor for increased seizure frequency. A study of 433 epilepsy patients by Thaper et al., modelling the relationship between stress, anxiety and depression with the occurrence of seizures, reported that depression was the only significant predictor for seizure frequency [57]. The potential psychotropic effect of some AEDs should also be borne in mind when treating depressive patients. Polypharmacy and certain AEDs, such as phenobarbital, have documented links to depression [6,58]. The possible implication of iatrogenic factors in causing or aggravating psychiatric problems emphasizes the need for regular medication reviews to proactively assess for the development of AEs, and supports recommendations for reducing levels of polypharmacy in epilepsy patients whenever possible [59,60].

The safety and tolerability results of these subanalyses highlight some of the challenges encountered in clinical practice when treating patients with comorbidities. In common with previous studies [61,62], focal epilepsy patients who presented with intellectual disability or psychiatric disorders, including those specifically with depression, experienced more AEs and were more likely to discontinue ESL treatment due to AEs compared with those without comorbidities. This is perhaps unsurprising since polypharmacy and coexisting disabilities, such as physical incapacities, autistic traits, psychological disorders and behavioral problems, are common in epilepsy patients with intellectual disability and psychiatric comorbidities [3,18,63]. Overall, the types of AEs reported in these subanalyses (most commonly, dizziness, fatigue and somnolence) were similar to those described in the primary Euro-Esli study and previous clinical trials [30–35,41]; no new safety signals were detected in patients with intellectual or psychiatric comorbidities. It is worth noting, however, that patients with intellectual and psychiatric comorbidities were twice as likely to experience hyponatremia as those without. This might be due to an additive or interactive effect from concomitant medications. Although, in this study, hyponatremia was not reported in any of the patients with depression concomitantly taking SSRIs or SNRIs, the use of antidepressants is still a plausible explanation for the increased rate of hyponatremia in this specific patient group, especially since SSRIs and other antidepressants themselves have documented links to hyponatremia [64]. Further studies are therefore warranted to elucidate potential drug–drug interactions or combinations that may increase the risk of hyponatremia in patients with intellectual and/or psychiatric comorbidities.

Patients with psychiatric comorbidities are susceptible to psychiatric and behavioral AEs [65]. A recent study, in which the medical records of 4085 epilepsy patients were analyzed, reported that psychiatric and behavioral AEs occurred in 17.2% of patients and that a history of psychiatric conditions was associated with increased incidence of psychiatric and behavioral AEs [66]. In the current Euro-Esli subanalyses, there were no significant differences in the incidence of psychiatric and cognitive AEs in patients with psychiatric comorbidities compared with those without, or in the subgroup of patients with depression and those without. Furthermore, the incidence rates of psychiatric AEs reported for patients with psychiatric comorbidities and those specifically with depression (3.7% and 4.4%, respectively) were lower than the rates documented for other AEDs. For example, in follow-up studies of epilepsy patients treated with topiramate and levetiracetam, 23.9% (103/431) and 10.1% (52/517) experienced psychiatric AEs, respectively [25,26].

Previous studies have also suggested that epilepsy patients with intellectual disability are more prone to psychiatric, behavioral and cognitive AEs compared with epilepsy patients at large [11,63,67]. In the current analyses, there was no significant difference in the incidence of cognitive AEs in patients with intellectual disability compared with those without, although a higher proportion of patients with intellectual disability experienced psychiatric AEs compared to those without. Nonetheless, the incidence of psychiatric AEs in patients with intellectual disability reported in this study (6.1% [6/99]) was relatively low compared with the incidence of psychiatric AEs reported for other AEDs [25,26]. Moreover, in a recent retrospective study by Jalihal et al., it was reported that ESL did not result in significant psychiatric and behavioral AEs in patients who previously discontinued levetiracetam treatment due to these side effects ($n = 26$) [29]. Taken together, these results suggest that ESL could be considered as a treatment option in patients who develop psychiatric and behavioral AEs with other AEDs [29]; however, regular follow-ups are warranted to assess the risk of psychiatric AEs throughout ESL treatment especially if intellectual disability is also documented.

Retention on ESL treatment was lower in patients with intellectual and psychiatric comorbidities, including in patients who specifically had depression, compared with those without these comorbidities. Lack of effectiveness and poor tolerability were the main reasons for discontinuation in these patient groups. Discontinuation of ESL treatment due to AEs was higher in patients with intellectual and psychiatric

comorbidities, and in those with depression, compared to those without. These results are consistent with previous studies since intellectual and psychiatric comorbidity in patients with epilepsy have been associated with decreased response to AED treatment and a worsened AEs profile [11,68,69].

The increased incidence of AEs noted in patients with versus without comorbidities, together with other clinical challenges, such as, physical disabilities or behavioral problems, can negatively affect QoL. The safety/tolerability profiles of AEDs have been reported as a principle determinant of QoL [70,71]. In order to minimize AEs, different strategies have been suggested; these include co-therapy reduction [60], employing monotherapy at the lowest effective dose if possible [59] and utilizing drug-sparing therapies when feasible [70]. Screening for AEs, as part of regular clinical reviews, may increase identification and guide AED treatment, which may, in turn, have a positive impact on patients' QoL [71].

The current study was limited in comprising subanalyses of Euro-Esli, which was itself a retrospective pooled analysis. In addition, there was great heterogeneity in the studies included in Euro-Esli and the information they reported [41]. Furthermore, diagnostic information for psychiatric and intellectual comorbidities was extracted from medical records and therefore not uniformly defined and verified across the studies included in Euro-Esli. The fact that the Euro-Esli study and these subanalyses have included large cohorts of patients, however, has allowed for meaningful statistical analyses to be conducted. This has permitted the effects of ESL in clinical practice to be elucidated in patients with intellectual and psychiatric comorbidities – patients who are otherwise not routinely included in clinical trials. Another potential limitation is the fact that confounding factors, e.g. the presence of psychiatric comorbidities at baseline in the intellectual disability group, were not recorded. Further studies are therefore needed to elucidate the potential effects of such confounding factors on the effectiveness and safety outcomes of ESL.

5. Conclusion

The results presented in this paper demonstrate that ESL is effective and generally well tolerated in epilepsy patients with intellectual and psychiatric comorbidities, including those specifically with depression. However, they also illustrate some of the difficulties encountered in clinical practice when treating these patients. Patients with comorbid intellectual disability and psychiatric disorders tend to be inherently more susceptible to AEs due to complex interactions between different factors, such as underlying etiologies, the presence of other comorbid conditions and concomitant medication use. Adapting a patient-centric approach to treatment is therefore essential in these patients to ensure that treatment goals are not limited to achieving seizure control but instead extended to improving patients' QoL.

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Compliance with ethical standards

The Euro-Esli study protocol was approved by the Ethics Committee of the Hospital Universitario y Politécnico La Fe, Valencia, Spain, as an extension of the local audit and the study was carried out in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All patients included in Euro-Esli provided informed consent before entering the study.

Declaration of conflict of interest

CPD is part of speakers' bureau of Eisai and UCB.

SR has received speaker and/or consultant fees from Eisai, GW Pharma, Idorsia, LivaNova, and UCB pharma.

GA and GB have no conflicts of interest.

JC has received speaker's honoraria and/or consultancy fees from Bial and Eisai.

RM is a current employee of Eisai Europe Ltd.

VV has participated in advisory boards and pharmaceutical industry-sponsored symposia for Eisai, UCB Pharma, Merck Sharp & Dohme, Bial, Pfizer, GSK, Esteve, Novartis, Medtronic, and Cyberonics.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jns.2019.04.040.

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