Safety profile of the newest antiepileptic drugs: a curated literature review

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Running title

Safety of newest antiepileptic drugs.

Abstract

Despite the introduction of new antiepileptic drugs (AEDs), the quality of life and therapeutic response for patients with epilepsy remains unsatisfactory. In addition, whilst several antiepileptic drugs (AEDs) have been approved and

consequently marketed in recent years, little is known about their long-term safety and tolerability. Availability of the newest AEDs, characterized by improved pharmacokinetic profiles, has positively impacted upon the treatment approach for patients with partial seizures in clinical practice. However, the main cause of treatment failure is still poor patient compliance due to the occurrence of adverse drug reactions (ADRs) that lead to treatment withdrawal in about 25% of cases before achieving maximal efficacy, and is associated with increasing health care costs.

Early detection of ADRs could lead to an improvement in patients' quality of life. In this Review, we conducted an online database search using Medline, PubMed, Embase, and the Cochrane Online Library to review the available studies highlighting the clinical relevance of side effects, pharmacological interactions, safety and tolerability of the newest AEDs: Brivaracetam (BRV), Cannabidiol (CBD), Eslicarbazepine acetate (ESL), Lacosamide (LCM), and Perampanel (PER).

Keywords:: antiepileptic drugs, adverse drug reactions, tolerability, safety, interactions, clinical trials, metanalysis, pooled analysis.

Introduction

Approximately one-third of all patients with epilepsy do not become seizure-free, despite treatment with two or more antiepileptic drugs (AEDs) at a maximal tolerated dose [1-4]. Several new AEDs have been approved and placed on the market in recent years, however limited information is available regarding their long-term safety profiles at the time of approval.

Whilst newer AEDs have a better pharmacokinetic profile compared to more historic drugs, the main cause of treatment failure remains poor adherence due to the onset of adverse drug reactions (ADRs), leading to treatment withdrawal in about 25% of cases before achieving effective dose levels, repercussions of which include increased health care costs [5, 6]. Furthermore, although AED-related ADRs are a major source of disability, morbidity, and mortality [7], as well as one of the strongest predictors of unsatisfactory health-related quality of life (independent of seizure outcome [5]), it is only recently that post-marketing surveillance has been recognized as an important step needed to assess the relevance of AEDs in clinical practice. Early detection of ADRs may lead to an improvement in patients' quality of life [5, 8]. Most AEDs have a narrow therapeutic index and influence drug metabolizing enzyme activity. In addition, as many AEDs are also substrates of the enzymes involved [9-11], clinically relevant drug interactions between AEDs and other drugs may play an important role related to commonly reported ADRs [9, 10, 12, 13].

In this Review, we discuss the safety profiles of newest AEDs (Brivaracetam (BRV), Cannabidiol (CBD), Eslicarbazepine acetate (ESL), Lacosamide (LCM), and Perampanel (PER)) highlighting the clinical relevance of side effects and pharmacological interactions.

Methods

We conducted an online database search using Medline, PubMed, Embase, and the Cochrane Online Library to review the available studies on the safety and tolerability of the newest AEDs. The words used in this search included brivaracetam, cannabidiol, eslicarbazepine, lacosamide, perampanel, and were assessed for association with additional search terms including adverse reaction, treatment-emergent adverse events (TEAEs), serious adverse reaction, and withdrawal.

Brivaracetam

BRV, approved in 2016 in the EU as an adjunctive therapy for the treatment of partial-onset seizures (POS), is an analogue of levetiracetam (LEV) with greater selectivity and 15- to 30-fold higher affinity than LEV for binding to synaptic vesicle protein 2A. BRV also inhibits voltage-dependent sodium currents [14] and reverses the inhibitory effects of negative modulators on gamma-amino-butyric-acid (GABA) and glycine induced currents [15]. However, inhibition of excitatory neurotransmission may result in dysfunction in some areas of the central nervous system (CNS) associated with cognitive

and/or motor function impairment [16]. BRV displays linear and dose-proportional pharmacokinetics with low inter-individual variability [16, 17]. The drug is rapidly absorbed following oral administration, with a T_{max} ~ 1 hour. The metabolic clearance of BRV is increased in a time-dependent manner at supratherapeutic doses and steady state is reached within 1 week. BRV plasma protein binding is weak (20%) with a volume of distribution of 0.6 L/kg. The terminal elimination half-life of BRV is approximately 8 h [18]. The major metabolic pathway of elimination involves hydrolysis of the acetamide group with consequent formation of an acid metabolite. A minor pathway, mainly mediated by cytochrome P450 (CYP450) 2C19, leads to the formation of a hydroxy metabolite [19]. Both metabolites are inactive. To date, a wide-range of preclinical studies have reported the effectiveness of BRV in partial and generalized seizures. BRV has also demonstrated efficacy in reducing the frequency of POS in six randomized, placebo (PBO)-controlled trials [20-25]. Moreover, two meta-analyses highlighted the efficacy of BRV as an add-on treatment for patients with uncontrolled partial seizures.

Safety profile of BRV

A previous meta-analysis involving two dose-ranging Phase II studies showed that BRV may be effective and well tolerated as an adjunctive treatment in patients with refractory partial seizures, and discontinuations due to TEAEs were infrequent (PBO 3.7%; BRV 2.6%) [26, 27]. Four randomized controlled trials (RCTs) compared BRV 50 mg versus PBO [20-23], and one compared BRV 200 mg versus PBO [24]. One BRV study used a flexible-dose of BRV, ranging from 20 to 150 mg [25]. TEAEs were mostly CNS-related, appearing to be transient and decreasing in intensity during the course of treatment. In the RCTs mentioned above, 1,639 patients were included in an intention-to-treat analysis (1,214 treated with BRV and 425 with PBO) and no differences were noted in the proportion of patients experiencing at least one ADR (65.5% with BRV vs 60.5% with PBO, P=0.10). Most ADRs reported were of mild or moderate intensity; overall withdrawal rate due to ADRs was low and similar in BRV and PBO groups (5.4% with BRV vs 4.2% with PBO, P=0.37). Serious ADRs were quite rare and equal between BRV and PBO groups (2.9% with BRV vs 4.4% with PBO, P=0.16). Fatigue and somnolence were more frequently observed in the BRV group compared to PBO. Irritability was reported in three studies only, and it was present in a small proportion of subjects (3% receiving BRV, 1% receiving PBO, P=0.36) [28]. Efficacy and safety of BRV was analyzed in three recent meta-analysis. Tian et al. [29] conducted a meta-analysis to evaluate the efficacy and safety of different doses of BRV. The data, inclusive of reports from five trials, showed that both fatigue and nasopharyngitis were significantly associated with 20 mg BRV, irritability and fatigue were associated with 50 mg BRV, and somnolence was associated with 150 mg BRV, whereas no significant differences were noted for the other common TEAEs, concluding that BRV was fairly well tolerated by patients. Another meta-analysis showed significantly higher incidences of fatigue (2.05, 95% CI 1.19–3.53, P = 0.009) and somnolence (1.63,95% CI

1.08–2.45, $P = 0.02$) in patients treated with BRV. In particular, in different dosage subgroups, patients receiving 20 mg/d BRV had significantly higher incidences of nasopharyngitis (RR 5.98, 95% CI 1.36–26.34, $P = 0.02$) and fatigue (RR 3.00, 95%CI 1.20–7.47, $P = 0.02$), while patients receiving 50 mg/d BRV had significantly higher incidences of fatigue (RR 2.38, 95% CI 1.16–4.88, $P = 0.02$) and irritability (RR 2.95, 95%CI 1.03–8.44, $P = 0.04$). The overall withdrawal rate was not statistically different between BRV and PBO groups, regardless of the BRV dosage (RR 1.08, 95% CI 0.73–1.59; $P = 0.70$; heterogeneity: $P = 0.27$; $I^2 = 23\%$) [30]. Lattanzi et al. [31] conducted a meta-analysis including six trials involving 2,399 participants as per the intent-to-treat, 1,715 for BRV, and 684 for PBO. The TEAEs significantly associated with BRV were irritability (2.99 [1.28-6.97]), fatigue (2.19 [1.44-3.33]), somnolence (1.97 [1.45-2.68]) and dizziness (1.66 [1.19-2.31]). The overall risk ratio for treatment withdrawal due to TEAEs or an alternative reason were 1.58 (1.04-2.40) for BRV and 1.27 (0.93-1.73) for PBO. Furthermore, a post-hoc analysis of patients with secondarily generalized tonic-clonic seizures (SGTCS) from pooled data of three Phase III trials included a total of 487 subjects with baseline histories of SGTCS. The number of patients reporting TEAEs was similar between PBO (77/127) and BRV ≥ 50 mg/d (165/254) groups. Drug-related TEAEs were recorded in 100/254 patients receiving BRV ≥ 50 mg/d vs 41/127 receiving PBO. Ten patients (10/254) treated with BRV reported serious TEAEs. Discontinuation due to TEAEs occurred in 16/254 patients receiving BRV ≥ 50 mg/d versus 5/127 patients receiving PBO. The most frequently reported ADRs in the BRV group included somnolence (32/254), headache (28/254), dizziness (21/254), fatigue (20/254), and nausea (15/254). Four patients with a baseline history of SGTCS died. One patient was in the PBO group, two in BRV 200 mg/d group and one in BRV 50 mg/d group [32]. Such safety and tolerability data in the SGTCS safety population were consistent with data from the pooled phase III studies examining all focal seizure subtypes [33]. A pooled analysis from three phase III studies, that evaluated safety and efficacy of adjunctive BRV for focal seizures in older patients, was reported by Brodie et al. [34]. Data were pooled by treatment groups for the approved dose range of 50–200 mg/d: BRV 50, 100, 200 mg/d or PBO. This post-hoc analysis included patients aged ≥ 65 years. In this small subgroup of older patients treated with adjunctive BRV, a comprehensive evaluation of TEAEs revealed that 16/24 BRV patients reported TEAEs during the treatment period. Of these, 13/24 BRV patients reported drug-related TEAEs and 1/24 patients taking 100 mg/d BRV discontinued the study due to TEAEs. The most commonly reported TEAEs were headache (PBO 2/8 vs BRV 3/24), paresthesia (PBO 0/8 vs BRV 3/24), and somnolence (PBO 4/8 vs BRV 3/24). During the treatment period, one BRV-treated patient reported serious TEAEs, in particular the patient fell after a seizure. No drug-related serious ADRs or deaths were reported during the treatment period. Toledo et al. [35] conducted a pooled analysis considering phase IIb, III/IIIb and associated long term follow up studies. Of the 2,186 patients in the safety population, 1,848 reported ≥1 TEAEs and 1,184 patients reported ≥1 TEAEs that was considered to be treatment related. The most commonly reported TEAEs were headache in 457 patients, dizziness in 382 patients, somnolence in 333 patients,

nasopharyngitis in 288 patients and fatigue in 274 patients. The most frequently reported TEAEs (≥0.5%) leading to discontinuation were convulsions (31/2,186), somnolence (16/2,186), dizziness (14/2,186), depression (14/2,186), fatigue (12/2,186), suicidal ideation (11/2,186) and suicide attempt (10/2,186). Serious TEAEs were reported in 95/2,186 patients, in particular the most common were convulsions (56/2,186), status epilepticus (20/2,186), suicidal ideation (12/2,186), suicide attempt (12/2,186), pneumonia (12/2,186) and falls (10/2,186). Recently a meta-analysis evaluated the ADRs significantly associated with BRV treatment in a large selection of RCTs [36]. Eight RCTs with a total of 2505 patients were included in this meta-analysis, 1178 and 718 of which were randomized to BRV and PBO respectively. The number of serious ADRs was 73/1178 for patients randomized to BRV groups and 38/718 for patients randomized to PBO, even where no significant difference between BRV and PBO treatment groups was noted [RR 95% CI, 0.74 (0.50, 1.10); P = 0.13]. Furthermore, no significant difference in the withdrawal rate between the BRV and PBO groups was reported [RR 95% CI, 1.18 (0.84, 1.65); P = 0.34]. Fifteen ADRs (disturbance in attention, myoclonus, abdominal pain, grand mal convulsion, tremor, balance disorder, constipation, feeling cold, appendicitis, fall, hyporeflexia, middle insomnia, otitis externa, pyrexia, upper abdominal pain) were reported in no more than five subjects and considered rare. A total of 17 ADRs identified including dizziness [RR (99% CI) = 1.57(1.13, 2.18), P = 0.008], fatigue [RR (95% CI) = 1.98 (1.32, 2.97), P = 0.001], and back pain [RR (95% CI) = 0.44 (0.20, 0.93), P = 0.03] were significantly associated with BRV treatment. Moreover the authors conducted a subgroup analysis focused on drug dosage, showing that when compared with those receiving PBO, patients receiving 50 mg/d and 100 mg/d BRV had significantly higher incidences of fatigue ([RR (95% CI) = 2.27 (1.11, 4.63), P = 0.02], and [RR (95% CI) = 2.24 (1.15, 4.38), P = 0.02] respectively). Patients receiving 200 mg/d BRV had significantly higher incidences of dizziness [RR (95% CI) = 2.88(1.57, 5.30), P = 0.0007] and fatigue [RR (95% CI) = 3.02 (1.50, 6.06), P = 0.002]. Psychiatric ADRs with BRV were not higher than PBO [RR (95% CI) = 0.88 (0.60, 1.31), P = 0.54]. No effects on cardiac function were reported even at very high daily dosages (up to 800 mg/d) [37]. Behavioral ADRs after switching from LEV to BRV has been assessed in the study of Yates et al. [38]. Overall, 93.1% of the patients switched to BRV had a clinically significant reduction in behavioral ADRs, and 62% a complete remission at the end of the study. Also, a twice-daily dosing regimen might represent appropriate clinical practice in order to reduce drug fluctuations/peaks in blood plasma levels, and thereby possibly influencing the appearance of ADRs [16]. The rate of ADRs observed in these studies are summarized in Table 1.

Table **1.** Adverse reactions of BRV identified in RCTs.

Adverse reaction	**BRV 20**	**BRV 50**	**BRV 100**	**BRV 150**	**BRV 200**	**BRV 5-200**

Somnolence	5.8%[21] 14%[20] 8.1%[22]	5.8%[21] 16.8%[20] 9.4%[23] 6.1%[22] 16.6%[35] 11.5%[33]	 8.0%[22] 19.4%[24] 18.0%[35] 16.1%[33] 14.3%[34]	 5.8%[23] 13.8%[35]	 16.8%[24] 13.7%[35] 16.8%[33] 16.7%[34]	11.1%[25] 12.6%[32] 12.4%[36]
Dizziness	14%[20] 5.1%[22]	15.8%[20] 3.8%[23] 7.1%[22] 19.7%[35] 11.5%[33] 7.7%[21]	 5.0%[22] 16.5%[35] 10.3%[24] 8.8%[33]	 9.6%[23] 18.3%[35]	 15.4%[35] 14.4%[24] 14.4%[33]	8.6%[25] 8.3%[32] 9.5%[36]
Headache	3.8%[21] 6%[20] 14.1%[22]	1.9%[21] 12.9%[20] 15.1%[23] 18.2%[22] 24.8%[35] 16.0%[33]	 9.0%[22] 6.7%[24] 21.9%[35] 7.4%[33] 7.1%[34]	 7.7%[23] 22.6%[35]	 8.0%[24] 13.9%[35] 7.6%[33] 16.7%[34]	14.2%[25] 11%[32] 10.5%[36]
Fatigue	3.8%[21] 13%[20] 3.0%[22]	5.8%[21] 9.9%[20] 13.2%[23] 4.0%[22] 11.6%[35] 7.0%[33]	 8.0%[22] 10.7%[35] 7.5%[24] 7.6%[33]	 5.8%[23] 11.6%[35]	 11.2%[35] 11.6%[24] 11.6%[33]	7.8%[25] 7.9%[32] 8.8%[36]
Discontinuation Rate	1.9%[21] 4.0%[20] 4.0%[22]	1.9%[21] 5.9%[20] 3.8%[23] 5.1%[22] 21.9%[35] 5.0%[33]	 5.0%[22] 8.3%[24] 14.5%[35] 7.6%[33]	 3.8%[23] 8.4%[35]	 6.8%[24] 9.3%[35] 6.8%[33]	6.1%[25] 6.3%[32]

BRV interactions

BRV treatment does not appear to influence plasma concentrations of other AEDs [39]. In vitro, BRV inhibits epoxide hydrolase and, to a lesser extent, CYP3A4 and CYP2C19, and is a weak inducer of CYP3A4 [40]. However, it has been shown that BRV (400 mg/d) slightly reduced carbamazepine (CBZ) plasma concentration, while CBZ-epoxide levels increased in a dose-dependent manner due to BRV-induced epoxide hydrolase inhibition [41]. It is possible that other inducers including phenytoin (PHT), phenobarbital (PB) may exert similar effects. Coadministration with CBZ, PHT and PB has been shown to decrease BRV exposure by 26%, 21%, and 19%, respectively, however without significant effects

on response [42]. Rifampin, a potent CYP450 inducer, significantly decreased the AUC of BRV by 45% by CYP2C19 induction, therefore a dosage adjustment of BRV in patients on treatment with rifampin would be appropriate [43]. Conversely, gemfibrozil, a potent in vitro inhibitor of CYP2C9, did not influence the pharmacokinetics of BRV and its hydroxylation into BRV-OH [44]. A randomized, double-blind, placebo-controlled, two-way crossover study evaluated the interaction between BRV and a combination oral contraceptive showing that high doses of BRV (400 mg/d) caused a moderate decrease of ethinylestradiol and levonorgestrel plasma levels, but no impact on ovulation was reported [45]. A possible negative interaction between BRV and LEV has been reported in which concomitant use of LEV may reduce BRV efficacy; however, the data was derived from only a limited number of patients and may not be conclusive [20, 28]. The interactions between BRV and other drugs identified to date are summarized in Table 2.

Table **2.** Brivaracetam interactions.

AEDs	**Effect of AEDs on BRV**	**Effect of BRV on AEDs**
Oxcarbazepine		BRV increases Carbamazepine epoxide levels[41]
Carbamazepine	Carbamazepine decreases BRV AUC [42]	
Phenytoin	Phenytoin decreases BRV concentrations[42]	
Phenobarbital	Phenobarbital decreases BRV concentrations[42]	
OTHER (Non-AEDs) DRUGS		
Rifampin	Rifampin decreases the AUC of BRV[43]	
Ethinylestradiol–Levonorgestrel		BRV causes a moderate decrease of Ethinylestradiol and Levonorgestrel concentrations[45]

AED, antiepileptic drug; AUC, area under the plasma concentration–time curve; BRV, brivaracetam.

Cannabidiol

For many years cannabis (and some of its components) has been hypothesized as having potential antiepileptic effects. Preclinical studies show anticonvulsant activity of CBD in many animal models of acute seizure [46].

Recently, CBD has become particularly attractive because of a series of anecdotal reports that document the effectiveness of CBD in children with drug-resistant epilepsy [47]. However the exact mechanism by which CBD exerts its antiepileptic activity is still not completely clear [48, 49].

It has been demonstrated that the drug antagonizes with a higher potency both CB1 and CB2 receptors [50]. Furthermore CBD interacts with other non-endocannabinoid signaling systems and may therefore be considered a "multi-target" drug [51].

Recently, it has been reported that CBD might influence neuronal hyperexcitability by several mechanisms: decreasing the synaptic release of glutamate as a result of its antagonism on the G-protein-coupled receptor 55 (GPR55); activating 5-HT1a receptors [52, 53]; stimulating and desensitizing transient receptor potential of ankyrin type 1 (TRPA1) and of vanilloid type 1 (TRPV1) and 2 (TRPV2) channels [54, 55]; inhibiting the synaptic uptake of noradrenaline, GABA, adenosine as well as dopamine [56], and stimulating the activity of α3 and α1 glycine receptors [57, 58]. Moreover, further potential targets of CBD have been hypothesized: voltage-dependent anion channel 1 (VDAC1), nitric oxide (NO), peroxisome proliferator-activated receptor γ (PPAR-γ), tumor necrosis factor (TNF), cyclooxygenase (COX), fatty acid amide hydrolase (FAAH) and G-protein-coupled receptor (GPR) 18 [49]. Despite the extensive amount of preclinical data available, the current clinical evidence for the use of cannabinoids in human epilepsy is rather limited. Data concerning the clinical effects of CBD in human patients have been collected from anecdotal cases, phone or online surveys, epidemiological studies, and few clinical trials [46].

CBD is present in the therapeutic product Sativex approved in Europe and other countries (Canada, Switzerland, Australia, New Zealand, and Kuwait) [59].

CBD is currently in phase III development for Dravet syndrome, Lennox-Gastaut syndrome, tuberous sclerosis complex (TSC), and infantile spasms, and is designated an orphan drug by the FDA [60].

Safety profile of CBD

Despite the large compassionate use of CBD, particularly in children with drug-refractory epilepsy, the efficacy data available are still insufficient. Little is also known about its safety and side effect profile in animals and humans, and further suitably designed trials are needed [61]. Several publications of parental reports showed the efficacy of CBD-enriched cannabis extracts for children with Lennox-Gastaux, Dravet syndrome or with refractory epilepsy; CBD seemed to be tolerated well by patients and some reported added beneficial effects on sleep, alertness and mood [62-64]. In particular, parental reports of 117 patients with Lennox-Gastaut indicated that CBD helped to decrease seizure frequency and reported side effects were far less common during CBD exposure, with the exception of increased appetite (35/117). A high proportion of respondents reported improvement in alertness (83/117), sleep (62/117) and mood (73/117) during CBD treatment [62].

In an open-label interventional trial, CBD seemed to be well tolerated in most patients. ADRs were reported in 128 of the 162 patients in the safety group. They included: somnolence (41/162), decreased appetite (31/162), diarrhea (31/162),

fatigue (21/162), convulsion (18/162), increased appetite (15/162), status epilepticus (13/162), lethargy (11/162), weight gain (11/162), and weight loss (10/162). Serious ADRs were recorded in 20 of 162 patients and included status epilepticus, diarrhea, weight loss and pneumonia. In total, 11 patients had elevated liver function tests. Five patients had mild to moderate thrombocytopenia; only one patient had severe thrombocytopenia (8 × 109/L) that resolved when valproate was stopped. All patients with hepatic, platelet, or ammonia abnormalities were also taking valproic acid (VPA). One patient taking VPA also had hyperammonemia that led to CBD discontinuation. Somnolence or fatigue was more likely in patients whom were also taking clobazam. Diarrhea and weight loss were reported more often in patients taking more than 15 mg/kg/d of CBD. Only 5 patients stopped CBD treatment because of an ADR [65].

A recent study evaluated the efficacy and safety of CBD in patients with TSC. Twelve of 18 patients in this study experienced at least one ADR possibly related to CBD. One patient experienced diarrhea and weight loss and exited after 17 months while another patient had viral myocarditis unrelated to CBD and exited after 12 months. Most ADRs experienced in this study were temporary and of mild severity. ADRs were resolved through dose adjustments of CBD or concomitant AEDs. The most common ADRs were drowsiness (8/18), ataxia (5/18), and diarrhea (4/18). No serious ADRs related to CBD were reported by TSC patients in this study, and only three of 18 patients stopped CBD treatment [66].

A multicenter study to evaluate the efficacy of CBD-enriched medical cannabis for intractable pediatric epilepsy across five Israeli pediatric epilepsy clinics showed that CBD treatment produced a significant positive effect on seizure load. Most of the children (66/74) reported reduction in seizure frequency: 13 reported 75-100% reduction, 25 reported 50-75% reduction, 9 reported 25-50% reduction, and 19 reported <25% reduction. ADRs were reported by 34/74 patients, in particular seizure aggravation in 13 patients, somnolence/fatigue in 16 and gastrointestinal problems and irritability in 5 patients. Five patients reported aggravation of seizures leading to CBD withdrawal [67].

A small open-label case series recently investigated the potential effect of CBD in febrile infection-related epilepsy syndrome (FIRES) showing that 6 out of 7 patients' seizures improved in frequency and duration. In all patients, side effects were limited to dizziness (2/7), decreased appetite and weight loss (1/7), and nausea/ vomiting (1/7 supposedly unrelated to CBD). Four patients developed a persistent tremor but this appeared to be secondary to underlying CNS pathology rather than effect of CBD [68]. The rate of ADRs observed in these studies is summarized in Table 3.

Table **3.** Adverse reactions of CBD identified in available studies.

Adverse reaction	**CBD 1-20**	**CBD 15-25**	**CBD 25**	**CBD 25-50**
Somnolence or lethargy	22%[67]		44.4%[66]	25%[65]

Increased appetite				9%[65]
Decreased appetite		14%[68]	5.6%[66]	19%[65]
Weight increased				7%[65]
Weight decreased		14%[68]		6%[65]
Diarrhoea			22.2%[66]	19%[65]
Fatigue				13%[65]
Convulsion				11%[65]
Status epilepticus				8%[65]
Seizure aggravation	18%[67]			
Irritability			11.1%[66]	
Agitation or anxiety			16.7%[66]	
Ataxia			27.8%[66]	
Insomnia or poor sleep			11.1%[66]	
Dizziness		28.6%[68]		
Gastrointestinal problems	7%[67]			
Nausea/vomiting		14.2%[68]		
Discontinuation Rate	7%[67]	0% [68]	11.1%[66]	7%[65]

CBD interactions

CBD is extensively metabolized by CYP450 enzymes in the liver, in particular by the isoforms CYP3A4 and CYP2C19 [69]; furthermore, CBD is able to inhibit CYP2C19, CYP2D6, and CYP2C9, and may inhibit members of the CYP3 family [70-72] leading to potential pharmacologic interactions with other drugs [73, 74]. In animal models repetitive administration of CBD may induce members of the CYP2B family [51]. A pharmacodynamic animal study using maximal electroshock and audiogenic seizure models showed that CBD potentiated the anticonvulsant effects of PHT by two-fold, and discreetly potentiated the effect of PB. CBD also reduced the anticonvulsant properties of chlordiazepoxide, clonazepam, [75] and ethosuximide [75, 76]. An interaction between CBD and clobazam was reported recently in a group of 13 pediatric patients [74]. To date, interactions with other AEDs have not been reported, despite their potential to be metabolized by enzymes that are induced or inhibited by CBD. The interactions between CBD and other drugs identified to date are summarized in Table 4.

Table.**4** Cannabidiol interactions.

AED	Effect of CBD on AED
Phenytoin	CBD potentiates the anticonvulsant effects of Phenytoin [75]
Phenobarbital	CBD discreetly potentiates the anticonvulsant effect of Phenobarbital[75]
Chlordiazepoxide	CBD reduces the anticonvulsant effects of Chlordiazepoxide[75]
Clonazepam	CBD reduces the anticonvulsant effects of Clonazepam[75]
Ethosuximide	CBD reduces the anticonvulsant effects of Ethosuximide [75, 76]
Clobazam	CBD increases Clobazam plasma concentrations[74]

AED, antiepileptic drug; CBD, cannabidiol.

Eslicarbazepine

ESL is a third-generation member of the dibenzapine family, first approved in Europe by the EMEA in 2009 than in US by the FDA as adjunctive therapy in adults and in children above 6 years of age with POS with or without secondary generalization.

After oral administration, ESL is rapidly absorbed and then extensively metabolized by hepatic esterases to eslicarbazepine (S-eslicarbazepine), which is the major metabolite and largely responsible for its pharmacological effect, consisting in a reduction of membrane excitability due to the blockade of voltage-gated sodium channels (VGSC) [27].

This active metabolite has a linear pharmacokinetic profile, a low binding to plasma proteins (<40%), a half-life of 20-24 hours and is mainly excreted by kidneys as an unchanged form or as glucuronide conjugates. Currently, the drug is being evaluated for approval as initial monotherapy and is under investigation as a treatment in children with focal epilepsies, in patients with newly diagnosed focal epilepsies, and also in other neurological and psychiatric disorders [77].

Several studies have demonstrated that once-daily add-on treatment with ESL 800 and 1200 mg is effective and generally well-tolerated in adults with refractory POS [78-80].

Safety profile of ESL

Three Phase III double-blind studies were conducted to assess safety and tolerability of ESL (400 or 800 mg once daily up to 1,200) as an add-on drug in focal epilepsies [81, 82]. The data obtained from a total of 1,049 patients randomized in these three studies have been subsequently pooled and analyzed by Gil-Nagel et al.[78]. Neurological ADRs were most common, such as somnolence (21/196 patients administered with 400 mg/d; 26/199 patients administered with 800 mg/d;

31/200 patients administered with 1200 mg/d; compared to 19/202 in PBO group), dizziness (26/196 patients administered with 400 mg/d; 44/199 patients administered with 800 mg/d; 57/200 patients administered with 1200 mg/d; compared to 12/202 in PBO group), headache (17/196 patients administered with 400 mg/d; 24/199 patients administered with 800 mg/d; 30/200 patients administered with 1200 mg/d; compared to 15/202 in PBO group), and nausea (10/196 patients administered with 400 mg/d; 16/199 patients administered with 800 mg/d; 20/200 patients administered with 1200 mg/d; compared to 5/202 in PBO group) [78]. Other reported ADRs were abnormal coordination, vomiting, diplopia, vertigo, diarrhea, ataxia, and fatigue [78]. One of these studies [81] reported that the incidence of possibly related psychiatric disorders was very low and consisted of anxiety, depression, insomnia, irritability, but they seemed not to be dose-related; the incidence of rash reported as a TEAE was low; 1 patient in the PBO group died during the study (from hypothermia). In the other study [82], different psychiatric symptoms such as agitation and apathy were reported, but no reports of suicide; rash was uncommon only in 3 out of the 295 patients treated with ESL, and hyponatremia was reported as a TEAE in 4 ESL patients (ESL 1200mg: n = 2; ESL 800mg: n = 1; ESL 400mg: n = 1), but not in PBO patients. In the third study [80] rash and hyponatremia occurred in 3 and 1 out of the 165 patients treated with ESL respectively; in both studies [78,80] no deaths during treatment were reported. The results of these trials demonstrated that adjunctive ESL, once-daily at doses of 800 and 1200 mg/d is efficacious and well tolerated as a therapy in drug-resistant focal epilepsies [78], although the increase in the dose of ESL increased the overall incidence of TEAEs. Specifically, a higher incidence of diplopia, nausea, abnormal coordination, dizziness, headache, and somnolence in the 800 and 1200 mg ESL groups was reported, with some of those TEAEs leading to study discontinuation (mainly vertigo, diplopia, blurred vision, nausea and vomiting, fatigue, abnormal coordination, dizziness, headache, and somnolence) in a dose-dependent manner, with a total discontinuation rate for ESL patients of 14% [78]. Two open label extension (OLE) studies [83, 84] in 639 patients completing Phase III trials [81, 82] were performed to evaluate the long-term tolerability and safety of ESL Patients started with a once-daily 800 mg dose of adjunctive ESL to a stable dose of concomitant AED for 4 weeks, with the possibility of an up/down titration between 400 and 1200 mg to individualize therapy.

There was no predetermined fixed-dosing regimen in these studies, ESL doses were individualized at the investigator's discretion within the 400-1200mg dose range. Exposure data indicated that most patients were administered ESL 800 mg once-daily, suggesting that this dosage appeared to offer the optimal maintenance add-on treatment regimen for most patients [83, 84]. In the first OLE study, a total of 314 patients were enrolled [83]. The most frequent TEAEs were headache and dizziness (32 patients each), diplopia (in 17 patients), and nasopharyngitis (in 16 patients); vertigo, somnolence and nausea occurred in 12, 11 and 10 patients respectively, rash occurred in 3 patients. TEAEs led to premature study discontinuation for 11 patients, and no deaths were related to study medication.

A total of 325 patients were enrolled in the second OLE trial [84]. As in the previously reported randomized study [82], the most frequently reported ADRs were dizziness (in 86 patients), headache (in 51 patients), somnolence (in 39 patients), abnormal coordination, diplopia and decreased diastolic blood pressure (in 28 patients each), vomiting (in 22 patients), nausea (in 21 patients), nasopharyngitis (in 20 patients), diarrhea (in 18 patients), blurred vision (in 17 patients), fatigue, hypotension and insomnia in a lower number of patients; rash occurred in 4 patients while three patients died during the study. Thirty-seven patients discontinued due to TEAEs.

Several recent retrospective studies have also confirmed the safety of ESL in patients with focal epilepsies of differing severities [85-87]. In particular, some of these studies showed an apparently better tolerability during ESL treatment after switching from oxcarbazepine (OXC) at a dose ratio of 1:1, whilst switching from CBZ to ESL did not reduce ADRs [87]. However, all these findings require confirmation by further studies. Recent data resulting from a network meta-analysis that compared the tolerability profile of ESL, LCM and OXC from double-blind, PBO-controlled trials, showed that at high recommended doses, patients treated with OXC withdrew from the experimental treatment more frequently than patients treated with ESL and LCM. Furthermore, some vestibulo-cerebellar ADRs (abnormal coordination and diplopia) were significantly more frequently observed in patients treated with OXC than in patients treated with LCM and ESL [88].

Behavioral and psychiatric disorders (e.g. agitation, anxiety, depression, and even suicide ideation) are frequent in patients with drug-resistant focal epilepsies, and in some cases can be related to pharmacological treatment [89]. However, the incidence of psychiatric ADRs was low in clinical studies with ESL [78]. The incidence of rash, which represents the most common idiosyncratic of all ADRs [90] seemed to be low in patients treated with ESL (~1% in all Phase III ESL studies) [78]. Hyponatremia during ESL treatment, has been observed in 0.6%-1.3% of patients in premarketing clinical trials [78], whilst others report it in 1.2% [84] and 2.7% [86] of patients respectively. However, the frequency of hyponatremia in patients under treatment with ESL needs to be assessed in more detail by further studies. Lastly, prolongation of the P-R electrocardiographic interval has been observed in clinical studies, so caution should be exercised in patients with medical conditions such as low levels of thyroxine, or cardiac conduction abnormalities, or when taking concomitant drugs known to be associated with P-R prolongation [91].

Very limited information is available regarding the safety of ESL in the pediatric population. The only published trial in a small pediatric population of drug-resistant patients [92] showed a dose dependent pattern of tolerability of this AED similar to that observed in adults, with most frequent ADRs characterized by somnolence, diplopia, vomiting, disequilibrium and dizziness. The rate of ADRs observed in these studies is summarized in Table 5.

Table **5.** Adverse reactions of ESL identified in RCTs.

Adverse reaction	**ESL 400**	**ESL 800**	**ESL 1200**	**ESL 400 – 1200**
Dizziness	13.3%[78]	22.1%[78]	28.5%[78]	18.5%[83, 84]
Somnolence	10.7%[78]	13.1%[78]	15.5%[78]	7.8%[83, 84]
Headache	8.7%[78]	12.1%[78]	15.0%[78]	13%[83, 84]
Nausea	5.1%[78]	8.0%[78]	10.0%[78]	4.8%[83, 84]
Vertigo	2.0%[81]	2.0%[81] 2.4%[80]	5.9%[81] 3.8%[80]	3.8%[83]
Diplopia	2.0%[81] 8.3%[82]	7.1%[81] 14.9%[82] 1.2%[80]	10.8%[81] 10.2%[82] 3.8%[80]	7%[83, 84]
Abnormal Coordination	5.2%[82]	12.9%[82] 2.4%[80]	11.2%[82] 5.0%[80]	8.6%[84]
Vomiting	4.2%[82]	12.9%[82] 4.7%[80]	10.2%[82] 7.5%[80]	
Vision blurred	7.3%[82]	7.9%[82]	7.1%[82]	5.2%[84]
Fatigue	4.2%[82]	5.0%[82]	7.1%[82]	
Diarrhea		3.5%[80]	2.5%[80]	5.5%[84]
Nasopharyngitis				5.6%[84]
Discontinuation Rate				3.5%[83] 11.4%[78] 14%[78] 16.2%[86] 50%[87]

ESL interactions

ESL is generally administered at a dose of 400mg once daily up to 1200mg once daily and has a low potential for drug-drug interactions [77]. As ESL has been shown to be a weak inducer of cytochrome P450 CYP3A4 and UDP-glucuronyl transferases in vitro, an increase in the dose of medicinal products which are mainly metabolized through these metabolic pathways may be required when co-administered with ESL [93]. ESL also has inhibiting properties with respect to CYP2C19, that might require dose adjustments of co-administered drugs metabolized by this enzyme, such as PH, diazepam, omeprazole, and clopidogrel [93]. Regarding interactions with other AEDs, data from healthy subjects have shown that co-administration of ESL 1,200 mg once daily with enzyme inducers PH or CBZ resulted in an average decrease of 31%-33% in exposure to ESL, most likely caused by an induction of glucuronidation [93]. Meanwhile, an average increase of 31%-35% in exposure to PH, most likely caused by an inhibition of CYP2C19 was also observed in these subjects, suggesting that a reduction in the dose of PH may be necessary during coadministration [93]. Similar

studies showed less pharmacokinetic interactions between ESL and topiramate (TPM), and ESL and lamotrigine (LMG) [93], although a more recent report of an analysis of population pharmacokinetic data revealed that LMG mean plasma concentrations decreased by 25% during concomitant ESL administration [78], probably due to an interaction at the level of renal elimination and/or hepatic metabolism.

Regarding other drugs, administration of ESL 1200 mg once daily to female subjects using a combined oral contraceptive showed an average decrease of 37% and 42% in systemic exposure to levonorgestrel and ethinylestradiol respectively, most likely caused by an induction of CYP3A4 [94]. Data from healthy subjects have shown a reduction of systemic exposure to simvastatin and rosuvastatin (50% and 36%-39%, respectively) when co-administered with ESL [93]. Moreover, co-administration of ESL with warfarin was found to cause a mild (23%) but statistically significant decrease in (S)-warfarin plasma exposure, with no significant effect on coagulation [95]. No interaction has been observed between digoxin and ESL in healthy volunteers [93]. The interactions between ESL and other drugs identified to date are summarized in Table 6.

Table **6.** Eslicarbazepine interactions.

AEDs	Effect of AED on ESL	Effect of ESL on AED
Topiramato	Topiramate decreases ESL plasma concentrations[93]	
Carbamazepine	Carbamazepine decreases Cmax and AUC of ESL[93]	
Lamotrigine		ESL decreases Lamotrigine plasma concentrations [78, 93]
Phenytoin	Phenytoin decreases AUC and Cmax of ESL[93]	ESL increases AUC and Cmax of Phenytoin[93]
OTHER (Non-AED) DRUGS		
Simvastatin		ESL decreases Cmax and AUC of Simvastatin[93, 145]
Warfarin		ESL decreases (S)-warfarin plasma concentration[95]
Levonorgestrel-ethinylestradiol		ESL decreases levonorgestrel and ethinylestradio AUC[94]

AED, antiepileptic drug; AUC, area under the plasma concentration–time curve; Cmax, maximum plasma concentration; ESL, eslicarbazepine.

Lacosamide

LCM is a synthetic chiral derivative of the amino acid D-serine approved by the EMA in August 2008 as an adjunctive treatment for partial-onset seizures in patients aged ≥16 years, and later by the US FDA as well in patients aged ≥17 years [27]. LCM appears to have a dual mode of action: selective enhancement of sodium channel inactivation that may help normalize activation thresholds and decrease neuronal hyper-excitability, and modulation of collapsin response mediator protein-2 (CRMP-2) that may contribute to decreased neuronal loss by providing neuro-protective effects. Rapidly and completely absorbed after oral administration, LCM has a high oral bioavailability (approximately 100%) and demonstrates minimal protein binding (<15%). Peak plasma levels occur approximately 1 to 4 hours after dose administration, and the elimination half-life is about 13 hours. LCM also has a low potential for drug interactions. LCM and its major metabolite are eliminated primarily by the kidney [96]. Results from completed trials suggest that an optimal LCM dose is in the range of 200 to 600 mg/d [96]. A trial conducted in the US confirmed that LCM is efficacious at dosages of 400 and 600 mg/d, but has a more favorable safety profile at a 400 mg/d dose level; a European/Australian trial established the efficacy and tolerability of both 200 and 400 mg/d LCM [97]. LCM is currently approved at dosages up to 400 mg/d as a monotherapy or adjunctive therapy in adults (17 years or older) with POS in the US and as an adjunctive therapy in adults (16 years or older) with POS in the European Union and other countries [98].

Safety profile of LCM

To evaluate the safety, tolerability and efficacy of LCM, three pivotal phase II/III trials were performed in adults patients with refractory focal epilepsies and uncontrolled POS [99-101]. During these multicenter, double-blind, PBO-controlled trials, a total of 1308 patients were randomized to PBO or LCM at different daily doses in the range of 200-600 mg/d. Initially, the first IIb multinational trial evaluated LCM 200, 400 or 600 mg/d compared with PBO as adjunctive treatment in 418 adults taking one or two AEDs with or without additional vagus nerve stimulation (VNS) [99]. Two further additional phase III trials [100, 101] were conducted in parallel, to confirm these results in an expanded population of patients taking up to three AEDs with or without additional VNS, and evaluating LCM 200 mg/d and 400 mg/d compared to PBO in a total of 890 randomized patients. Furthermore, patients who completed the double-blind trials SP754 [100] and SP755 [101], and decided to continue LCM treatment were enrolled to participate in two OLE trials to assess the long-term (up to 5 and 5.5 years of exposure, respectively) safety of LCM as adjunctive therapy [102, 103].

Data pooled [104] from three similarly designed randomized, double-blind, PBO-controlled trials [99-101], in whom a total of 1308 patients were randomized to receive fixed dosages of LCM (200 mg/d, n = 270; 400 mg/d, n = 471; 600 mg/d, n = 203) or PBO (n = 364) were analyzed to evaluate the safety profile of LCM. Among all patients who received LCM at all doses (n = 944), the most frequently reported TEAEs (occurring at an incidence of ≥10%) were dizziness (288 vs 77), headache (120 vs 83), nausea (107 vs 41), and diplopia (99 vs 8). Drug-associated TEAEs most commonly

involved the CNS (380), and all appeared to be dose-related. Incidence of TEAEs increased with increasing LCM dose: 44.1% for LCM 200 mg/d, 62.8% for LCM 400 mg/d, and 79.8% for LCM 600 mg/d, compared with 38.7% for PBO. One death was reported in the double-blind trials, although this was not considered to be related to the trial medication. During the treatment phase, TEAEs led to discontinuation in 17.1% of patients in the LCM group vs 4.9% of those on PBO. Dizziness and ataxia were the only two TEAEs that individually led to >5% of patients discontinuing from any LCM dose group. Discontinuations due to dizziness increased with increasing LCM dose. Other TEAEs of interest were rash, even if with a similar incidence for both LCM and PBO groups (27 vs 11 respectively), depression reported in 20 patients randomized to LCM (vs 2 patients in PBO group), and among TEAEs potentially related to cognition, only memory impairment occurred with an incidence of >2% across all doses of LCM [104]. Furthermore, evaluation of a large pool of cardiac safety data from a generally healthy population of adult patients with POS showed that treatment with adjunctive LCM at the maximum recommended dose (400 mg/d) was not clearly associated with any cardiac effect other than a small, dose-related increase in P-R interval that had no evident symptomatic consequences [105]. Later on, two OLE trials were performed to evaluate the long-term safety profile of LCM, by enrolling a total of 684 patients who underwent a blinded 2-week transition phase during which they were titrated to or maintained at a LCM dosage of 200 mg/d, with the possibility for the investigators to decrease the dose of LCM to 100 mg/d or increase it to a maximum of 800 mg/d at 100 mg/d weekly increments. Moreover, to optimize tolerability during the study, investigators were allowed to increase or decrease each patient's dose of concomitant AEDs and/or LCM, or discontinue concomitant AEDs to achieve LCM monotherapy. From a total of 308 patients enrolled in the SP756 trial [102], 138 patients completed the study, only 35 discontinued due to ADRs. Most common TEAEs related to trial medication (overall incidence >10%) involving a daily administration dose of 200 or 400 or 600 mg/d, and excluding other dosages included in the trial (100, 300, 500 and >600 mg/d), were dizziness, headache, nasopharyngitis and diplopia, occurring in 7, 6, 4 and 2 of 29 patients administered with LCM 200 mg/d respectively; 33, 11, 8 and 12 of 69 patients administered with LCM 400 mg/d respectively; and 36, 14, 19 and 10 of 64 patients administered with LCM 600 mg/d respectively. Other reported AEs were nausea, vomiting, balance disorder, tremor fatigue and nystagmus. Neither of the two deaths that occurred during the study was considered related to LCM treatment by the investigator. Finally, we calculated the overall incidence of the most common ADRs that occurred within the 200-600 mg/d LCM dose range. In the SP774 trial [103], 160 of 376 treated patients completed the study, whereas only 34 discontinued due to ADRs. During the study, the most frequently reported TEAEs (≥5% of patients) were dizziness (n=91), headache (n=54), diplopia (n=52) and nasopharyngitis (n=52). Other ADRs such as vertigo, somnolence, vomiting, tremor, fatigue, depression, balance disorder, were reported by fewer patients (<10%), moreover rash was reported by 14 patients, memory impairment by 13 patients and cognitive disorder

by 10 patients. Three patients died during the trial but all the deaths were considered not related or unlikely to be related to trial medication by the investigator.

In summary, the present data support the use of LCM as a long-term (up to 5 years) adjunctive treatment for POS in patients taking up to three concomitant AEDs [102, 103, 106]. Overall, LCM can be considered generally well tolerated, with mostly dose-dependent CNS and gastrointestinal related ADRs (dizziness, diplopia, somnolence, headache, nausea, and vomiting). It has been suggested that LCM prolongs the P-R interval, but symptomatic arrhythmias have only very rarely been reported [107]. The rate of ADRs observed in these studies is summarized in Table 7.

Table 7**.** Adverse reactions of LCM identified in RCTs.

Adverse reaction	**LCM 200**	**LCM 400**	**LCM 600**	**LCM 200 – 600**
Dizziness	15.9%[104] 24.1%[102]	29.5%[104] 47.8%[102]	52.7%[104] 56.3%[102]	30.6%[104] 47%[102] 24.2%[102, 103]
Headache	11%[104] 20.7%[102]	13.8%[104] 15.9%[102]	12.3%[104] 21.9%[102]	12.7%[104] 19%[102] 14.4%[102, 103]
Diplopia	6.3%[104] 6.9%[102]	10.4%[104] 17.4%[102]	16.3%[104] 15.6%[102]	10.5%[104] 14.8%[102] 13.8%[102, 103]
Nasopharyngitis	13.8%[102]	11.6%[102]	29.7%[102]	19%[102] 13.8%[102, 103]
Nausea	7.4%[104]	11.3%[104]	17.2%[104]	11.4%[104]
Vomiting	5.9%[104]	8.5%[104]	15.8%[104]	9.3%[104]
Fatigue	7.0%[104]	7.2%[104]	14.8%[104]	8.8%[104]
Blurred Vision	2.2%[104]	8.5%[104]	16.3%[104]	8.4%[104]
Abnormal Coordination	4.1%[104]	7.2%[104]	15.3%[104]	8.1%[104]
Tremor	3.7%[104]	6.2%[104]	11.8%[104]	6.7%[104]
Nystagmus	2.2%[104]	4.5%[104]	10.3%[104]	5.1%[104]
Balance disorder	1.1%[104]	5.1%[104]	6.4%[104]	4.2%[104]
Discontinuation Rate				17.1%[104] 13.2 %[146] 11.4 %[102] 9.0%[103]

LCM interactions

Low plasma protein binding (≤15%) and a low potential for pharmacokinetic drug–drug interactions has been demonstrated for LCM [108]. In healthy volunteers, LCM did not affect the plasma concentration of the CYP-450 enzyme

inducer CBZ or the CYP-450 enzyme inhibitor VPA; moreover, the plasma concentrations of LCM were not affected by CBZ or VPA [109]. In fact, no pharmacokinetic interactions were evident between LCM and CBZ, VPA, or oral contraceptives (ethinylestradiol/levonorgestrel) in dedicated studies [110]. LCM has also not been shown to have clinically relevant drug–drug interactions with midazolam [111], warfarin [112], omeprazole [113], digoxin [114], and metformin [108]. Furthermore, although LCM does not induce or inhibit CYP isoenzymes and therefore is not expected to be involved in pharmacokinetic interactions involving CYP450, a total of four pharmacokinetic interactions involving LCM and concomitant AEDs have been described to date. An abstract report of a population pharmacokinetic evaluation in subjects with POS enrolled in two Phase III, double-blind, multicenter, randomized, parallel group, PBO-controlled trials of LCM reported that, as a class, the enzyme-inducing AEDs (CBZ, PH, PB) increased LCM clearance values by ~36 % [115]. A subsequent study of 20 healthy male volunteers (aged 18–45 years) using a randomized, open- label, multiple-dose, two-treatment, two-group design reported that CBZ, administered as 200 mg twice daily, had no significant effect on the pharmacokinetics of LCM administered as 200 mg twice daily [116]. A double-blind, PBO-controlled study of adjunctive LCM in patients with partial epilepsy reported that patients co-prescribed OXC had mean plasma concentrations of 10-hydroxycarbazepine (the pharmacologically active metabolite of OXC) 15 % lower if they received a 400-mg/d dose of LCM, whilst at a dose of 200 mg/d LCM no effect was observed [101]. The mechanism of this interaction is unknown.

Moreover, in a case series of seven patients (2 males, 5 females; aged 22–77 years), LCM induced symptoms of neurotoxicity (diplopia, dizziness, and drowsiness) when concomitantly administered to voltage-gated sodium channel blocking AEDs, namely CBZ, PH and OXC. Symptoms of neurotoxicity ameliorated upon dose reduction [117]. Likewise, a single case report of a 4-year-old girl with refractory complex partial seizures showed signs of pharmacodynamic interaction between LCM and VPA resulting in toxicity [118]. Additional drug-drug interactions between LCM and other ADEs are summarized in Table 8.

Table **8.** Lacosamide interactions.

AEDs	**Effect of AEDs on LCM**	**Effect of LCM on AEDs**
Oxcarbazepine		LCM decrases10-hydroxycarbazepine concentrations [101]
Carbamazepine	Increase LCM clearance [115]	
Phenytoin	Increase LCM clearance [115]	
Phenobarbital	Increase LCM clearance [115]	

AED, antiepileptic drug; LCM, lacosamide.

Perampanel

PER is an orally administered, first-in-class, highly-selective noncompetitive AMPA-type glutamate receptor antagonist, approved in October 2012 by the FDA, for use as an adjunctive therapy in patients with refractory partial seizures associated with epilepsy [119, 120], and more recently by the EMA as an adjunctive therapy of primary generalized tonic clonic seizure (PGTCS), and idiopathic generalized epilepsy (IGE) in adults and adolescents over 12 years of age [121-123].

This compound has a novel mechanism of action that involves noncompetitive inhibition of the AMPA receptor resulting in decreased AMPA receptor-mediated glutamate signaling and decreased excitatory neuron activity, including seizure initiation and spread [120, 124]. PER is extensively metabolized via primary oxidation and sequential glucuronidation with involvement of cytochrome P450 CYP3A4 and/or CYP3A5. PER is absorbed from the gastrointestinal tract rapidly and completely; total absorption, concentration over 24 hours and the elimination half-life is not altered by food. Absolute bioavailability approaches 100% and pharmacokinetics are linear and plasma protein binding rate is 95%. The pharmacological profile appears superior and offers the possibility of once daily dosing due to the long half-life of PER [125].

Safety profile of PER

PER has been evaluated in an extensive clinical development program across a large, multinational population of patients with refractory partial-onset seizures. Key studies included two randomized, double-blind, placebo- controlled phase II dose-finding trials, in which the dose of PER was titrated up to 4 mg once or twice daily or 12 mg once daily [126], and three randomized, double-blind, placebo-controlled phase III registration trials, in which the dose of PER was titrated up to 8 or 12 mg once daily [127-129]. In all studies, patients were also receiving one to three concomitant AEDs. The efficacy and tolerability of PER as an adjunctive AED was investigated in patients with a 12 year history of POS in the phase III trials, and a pooled data analysis of these three trials have been published [130, 131]. Two studies [127, 129] compared maintenance doses of 8 and 12 mg, respectively, with PBO. The third trial [128] assessed doses of 2, 4 and 8 mg. All three studies led on to an extended open-label study that allowed a dose increase of up to 12 mg. PER was always started at 2 mg once daily and increased by 2 mg per week. Maintenance phases lasted 13 weeks. Thereafter patients were offered to enter a long-term open follow up with the possibility of a titration up to 12 mg PER *per* day. In Study 306 [128], target maintenance dosages were 2, 4 and 8 mg. The latter trial was performed in Europe, Asia and Australia. A total of 878 patients were recruited, and 712 (including 8 patients inappropriately randomized after failing screening) were randomized. Treatment groups comprised n = 185 in the PBO group, n = 180 in the 2 mg group, n = 172 in the 4 mg group and n = 169 in the 8 mg group. Study discontinuation due to an ADR occurred in 7 patients in the PBO group,

12 patients in the 2 mg/d group, 5 in the 4 mg/d group, and in 12 patients in the 8 mg/d group. In general, the most frequently occurring TEAEs (>5% in any treatment group) were dizziness (18/185 patients on PBO, 18/180 patients on PER 2 mg, 28/172 patients on PER 4 mg, 45/169 patients on 8 mg), somnolence (12/185 patients on PBO, 22/180 patients on PER 2 mg, 16/172 patients on PER 4 mg, 27/169 patients on 8 mg), headache (16/185 patients on PBO, 16/180 patients on PER 2 mg, 19/172 patients on PER 4 mg, 18/169 patients on 8 mg) and fatigue (5/185 patients on PBO, 8/180 patients on PER 2 mg, 13/172 patients on PER 4 mg, 9/169 patients on 8 mg). Upper respiratory tract infection, nasopharyngitis and gait disturbances were also reported but with less frequency. TEAEs that led to a discontinuation of the trial were reported in 7 patients receiving PBO, in 12 with 2 mg of PER, in 5 under 4 mg of PER and in 12 under 8 mg with adjunctive PER. The leading ADRs that were associated with treatment discontinuation were dizziness, convulsion, fatigue and vertigo, with a total discontinuation rate of 5.0% within any group receiving PER treatment.

In the multicenter trial Study 305 [129], the maintenance dosages of PER were 8 and 12 mg. A total of 496 participants were recruited and 389 randomized. One hundred and thirty-six patients were randomized to receive PBO and 129 were randomized to a maintenance dose of 8 mg PER and 121 to 12 mg PER. The most commonly reported ADRs with a frequency of more than 10% were dizziness (10/136 patients in the PBO group, 42/129 patients in the 8 mg/d group, 58/121 patients in the 12 mg/d group), somnolence (4/136 patients in the PBO group, 16/129 patients in the 8 mg/d group, 22/121 patients in the 12 mg/d group), fatigue (11/136 patients in the PBO group, 17/129 patients in the 8 mg/d group, 20/121 patients in the 12 mg/d group) and headache (18/136 patients in the PBO group, 11/129 patients in the 8 mg/d group, 16/121 patients in the 12 mg/d group). Of the TEAEs leading to discontinuation, the most frequent were dizziness, somnolence and convulsion, occurring in a total of 35 patients administered with 8 and 12 mg of PER. Most frequent ADRs that led to dose reduction or study discontinuation were dizziness, somnolence, headache, fatigue, ataxia and asthenia. In addition, a dose-response relationship seemed apparent with weight increase and irritability. The occurrence of falls was also more frequent in the PER groups than in the PBO group. Many of the patients with falls also complained of other CNS side effects such as unsteady gait, ataxia, dizziness, and slurred speech.

Study 304 [127] was the second multicenter, double-blind, PBO-controlled study assessing PER as an adjunctive therapy at maintenance doses of 8 and 12 mg. Patients were randomized according to a 1:1:1 ratio. A total of 534 patients were recruited and 390 randomized (including 2 patients inappropriately randomized after failing screening). The PBO was comprised of 121 patients, the PER 8 mg group comprised 133 and the PER 12 mg group comprised 134 patients. TEAEs led to discontinuation in 13% of the patients in the range of 8 - 12 mg of adjunctive PER. Most commonly reported adverse events with a frequency >10% were dizziness, somnolence, headache (again with a similarly high rate under PBO), falls, irritability and ataxia. No treatment-related deaths were reported. A meta-analysis of the phase II and III data indicated that, compared with PBO, PER 8 and 12 mg were associated with greater incidences of dizziness, while

somnolence was significantly higher at only 8 mg PER dose [132]. Other ADRs reported in ≥5% of patients treated with PER 4-12 mg in the phase III trials were fatigue, irritability, nausea and falls [133]. An increased incidence of falls was reported with PER compared with PBO in the phase III trials [133], and this risk of falls has been suggested to be associated with dizziness and somnolence [134]. Across the pooled phase III data, ADRs necessitated withdrawal of PER (at doses of 2-12 mg) in 9.5% of patients and 4.8% of patients on PBO. The ADRs most commonly leading to withdrawal were dizziness and somnolence. The ADRs typically resolved upon PER discontinuation [133]. The rate of allergic skin reactions was low and added up to 1.1% with 2 mg PER, 2.3% with 4 mg, 2.8% with 8 mg and 2.0% with 12 mg [133]. Psychiatric ADRs may be of special interest due to the mode of action of PER. Specifically, psychiatric and behavioral ADRs, including aggression, hostility, irritability, anger, and homicidal ideation and threats, have been reported in patients taking PER. During the transition to the OLE, PER was increased by 2 mg fortnightly and thus slower than in the phase III trials. Patients entering the extension study were up-titrated 2 mg every 2 weeks from the dose on which they finished the core study (or from 2 mg for patients previously on PBO) up to 12 mg/d or their individual maximum tolerated doses of PER. CNS ADRs occurred less frequently when the patients were up-titrated 2 mg every 2 weeks. During the conversion to the OLE, 91% of the patients who remained in the study reached doses of 10 or 12 mg/d [128]. Long-term results after an observation period of 3 years in 1216 patients who had been followed during this study have been published recently [135]. The most commonly reported ADRs with a frequency >10% were dizziness, somnolence, headache, fatigue, irritability and weight gain. Only dizziness and irritability led to the discontinuation of PER in more than 1% of all patients.

In a monocentric observational study [136], PER was administered once daily at bedtime, starting with 2 mg/d and increasing to 4 mg/d after 2 weeks. Patient were then maintained at this dose regimen for 4 weeks and a beneficial effect was noted in some cases. ADRs were reported in 40 patients. Leading side effects were somnolence (n = 31) and dizziness (n = 13) followed by ataxia, irritability, falls, cognitive decline and depression in single cases. Retention rate after 6 months was 70%. Another observational study was carried out in Germany and Austria with an identical design as the monocentric study reported above [137], comprising 281 patients who were treated with adjunctive PER. A total of 44 patients were on a monotherapy when PER was added. Baseline medication consisted of two AEDs in 124 cases, three AEDs in 62 patients and four baseline AEDs in the remaining 51 cases. After 6 months 169 patients were still on PER (a retention rate of 60%). The leading ADRs were somnolence in 70 patients and dizziness in 55 patients followed by ataxia in 11, aggression in 8, nausea in 7 and irritability in 6 patients. Tolerability was better in patients with one or two baseline AEDs. A recent publication from the UK reported on a series of 47 patients treated with adjunctive PER, at a median dose of 8 mg. The retention rate was 55%. In this study, psychiatric ADRs were reported with greater frequency than other ADRs [138]. The rate of ADRs observed in these studies is summarized in Table 9.

Table **9.** Adverse reactions of PER identified in RCTs**.**

Adverse reaction	**PER 2**	**PER 4**	**PER 8**	**PER 12**
Dizziness	10%[128]	16.3%[128]	26.6%[128] 32.6%[129] 37.6%[127]	47.9%[129] 38.1%[127]
Somnolence	12.2%[128]	9.3%[128]	16.0%[128] 12.4%[129] 18.0%[127]	18.2%[129] 17.2%[127]
Headache	8.9%[128]	11.0%[128]	10.7%[128] 8.5%[129] 15.0%[127]	13.2%[129] 13.4%[127]
Fatigue	4.4%[128]	7.6%[128]	5.3%[128] 13.2%[129]	16.5%[129]
Fall			9.8%[127]	12.7%[127]
Irritability			7.5%[127]	14.2%[127]
Ataxia			6.0%[127]	11.9%[127]
Discontinuation Rate				4%[128] 13%[127] 14%[129]

PER interactions

PER is mainly metabolized by CYP3A4 of the P450 enzyme system. At doses ≥ 8 mg/d, PER has weaker enzyme-inducing properties and may stimulate a more restricted range of CYP and/or UGT isoenzymes [11, 139, 140] therefore if may produce pharmacokinetic interactions with other drugs[141]. On the other hand, other AEDs including CBZ, OXC and phenytoin are inducers of CYP3A4, therefore they may influence pharmacokinetic of PER. For example, the clearance of PER has been reported to be increased by PHT or CBZ, two- and three-fold by respectively [27, 141]. In particular it has been shown, in a population pharmacokinetic analysis based on pooled data from PBO-controlled phase III clinical trials in patients taking PER, that CBZ increases PER clearance approximately 3-fold, while OXC or PH nearly 2-fold, while co-administered TPM increases PER clearance by approximately 20% [142]. To date no effects on PER clearance by LMG, VPA, LEV, clobazam, zonisamide, clonazepam, PB or primidone has been demonstrated [142]. Additionally, the clearance of other ADRs such as clonazepam, clobazam, LEV, PB, PH, TPM, CBZ, zonisamide, VPA and LMG did not change in a clinically significant manner with PER addition (12 mg/d), while OXC clearance revealed a 26% decrease [142]. Moreover, in an open-label drug interaction study, treatment with 6 mg PER for 20 days decreased midazolam AUC by 13%, and mean midazolam Cmax values by approximately 15% [143]. At dose levels of 4 mg or 8 mg, PER did not affect ethinylestradiol and levonorgestrel levels, but at the highest dose of 12 mg an increase of levonorgestrel was

observed and an 18% decrease in ethinylestradiol Cmax [141, 142]. The effect of PER on levodopa has been evaluated in an open-label study in 60 healthy volunteers taking PER 4 mg/d (days 2–20) and levodopa 100 mg showing that PER did not have a significant effect on the pharmacokinetics of levodopa [141]. Interaction between PER and ketoconazole has been examined in an open-label study of 26 healthy male volunteers receiving 400 mg ketoconazole once daily and 1 mg of PER. Ketoconazole increased mean PER AUC values by approximately 20% and prolonged the mean half-life by approximately 15% [144]. The interactions between PER and other drugs identified to date are summarized in Table 10.

Table **10.** Perampanel interactions.

AEDs	**Effect of AED on PER**	**Effect of PER on AED**
Oxcarbazepine	Oxcarbazepine decreases PER AUC[141]	PER increases Oxcarbazepine plasma concentrations[141]
Topiramato	Topiramate decreases PER AUC[141]	
Carbamazepine	Carbamazepine decreases Cmax and AUC of PER[141]	PER decreases Carbamazepine plasma concentrations[141]
Clobazam		PER decreases Clobazam plasma concentrations[141]
Lamotrigine		PER decreases Lamotrigine plasma concentrations[141]
Midazolam		PER decreases Midazolam AUC[141]
Valproic acid		PER decreases Valproic acid plasma concentrations[141]
OTHER (Non-AEDs) DRUGS		
Ketoconazole	Ketoconazole increases mean PER AUC[144]	

AED, antiepileptic drug; AUC, area under the plasma concentration–time curve; Cmax, maximum plasma concentration; PER, perampanel.

Conclusion

Several AEDs with different mechanisms of action, pharmacokinetics, efficacy and tolerability are now available for the treatment of epilepsy. In this review we considered five of the newest AEDs (namely BRV, CBD, ESL, LCM, PER) and collated the most relevant data on their safety and pharmacological interactions. At the time of writing, only few data were available on safety and these were primarily reported in the context of interactions with other drugs. The principal

benefit of the newest AEDs, in addition to reduced frequency and seizure severity, is the low number and severity of ADRs reported compared to more historic drugs.

Currently available information on the safety and tolerability of recently approved ADEs are primarily limited to the data obtained in RCTs, therefore they may not be fully representative of the true safety profile in the general patient population. Serious ADRs are often revealed a long time after time of approval, therefore it is important to stress on the need of close monitoring ADRs and adequately performing post marketing surveillance in the clinical practice setting, in order to increase the probability of detecting unknown of underreported ADRs which, in turn, will allow to firmly conclude on the overall safety of the newest antiepileptic drugs.

Conflict of Interest
None

Acknowledgements
None

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