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The efficacy of lacosamide as monotherapy and adjunctive therapy in focal epilepsy and its use in status epilepticus: clinical trial evidence and experience

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***Abstract*:** Lacosamide (LCM) is approved for anticonvulsive treatment in focal epilepsy and exhibits its function through the slow inactivation of voltage-gated sodium channels (VGSCs). LCM shows comparable efficacy with other antiepileptic drugs (AEDs) licensed in the last decade: in three randomized placebo-controlled trials, significant median seizure reduction rates of 35.2% for 200 mg/day, 36.4–39% for 400 mg/day and 37.8–40% for 600 mg/day were reported. Likewise, 50% responder rates were 38.3–41.1% for 400 mg/day and 38.1–41.2% for 600 mg/day. Similar rates were reported in post-marketing studies. The main adverse events (AEs) are dizziness, abnormal vision, diplopia and ataxia. Overall, LCM is well tolerated and has no clinically-relevant drug–drug interactions. Due to the drug's intravenous availability, its use in status epilepticus (SE) is increasing, and the available data are promising.

Keywords: epilepsy, lacosamide, monotherapy, partial-onset, seizure

Introduction

Epilepsy is a common and chronic neurological disorder that imposes a substantial burden on individuals, caregivers and society as a whole [Strzelczyk *et al.* 2008; Riechmann *et al.* 2015]. Antiepileptic drugs (AEDs) play a central and crucial role in treatment, as the majority of epilepsy patients require anticonvulsant treatment for an extended period of time. Because up to 30% of epilepsy patients are refractory to medical treatment [Kwan and Brodie, 2000; Kwan *et al.* 2011], the development of new therapeutic options is strongly warranted. Due to ongoing seizures, patients with drug-refractory epilepsy are affected by increased morbidity and mortality, social stigma, reduced employment opportunities and impaired quality of life for themselves and their caregivers [Smeets *et al.* 2007; Jacoby *et al.* 2011; Ryvlin *et al.* 2013; Riechmann *et al.* 2015]. Introduction of new AEDs provides an opportunity to achieve better seizure control for some of these patients [Luciano and Shorvon, 2007; Callaghan *et al.* 2011]. Furthermore, AEDs with an excellent efficacy and safety profile are needed for use as initial monotherapy as they might be continued for decades in patients [Glauser *et al.* 2013].

Lacosamide (LCM) was approved in 2008 in the European Union and in the USA as adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalization in adults and adolescents with epilepsy. LCM is licensed for adolescents older than 16 years in the European Union and older than 17 years in the USA. Additionally, the US Food and Drug Administration has approved LCM as monotherapy in focal epilepsy in 2014.

LCM is a functionalized amino acid with a distinct mode of action: the drug enhances the slow inactivation of voltage-gated sodium channels (VGSCs) [Doty *et al.* 2007, 2013]. In contrast, traditional sodium channel blockers affect the fast inactivation of VGSCs. The slow inactivation of VGSCs results in the stabilization of hyperexcitable neuronal membranes, the inhibition of neuronal firing, and the reduction of long-term

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channel availability without affecting physiological function [Doty *et al.* 2013].

LCM is available as film-coated tablets (50 mg, 100 mg, 150 mg, 200 mg), syrup (10 mg/ml) and solution (10 mg/ml) for intravenous infusion. Bioequivalence among the three LCM formulations has been demonstrated, allowing for direct conversion without titration [Cawello *et al.* 2012]. LCM exhibits several favorable pharmacokinetic characteristics as rapid absorption, high oral bioavailability (100%) not affected by food, linear and dose-proportional pharmacokinetics with low interindividual and intraindividual variability [Cawello *et al.* 2012, 2014a]. LCM has low plasma protein binding of less than 15%. LCM is metabolized by CYP2C19, CYP2C9, and CYP3A4 into the pharmacologically inactive O-desmethyl-LCM and undergoes primarily renal elimination with less than 1% of the dose eliminated in the feces [Cawello *et al.* 2012, 2014b]. LCM has an elimination half-life of 13 h, which supports a twice-daily dosing regimen. Steady-state plasma concentrations after each dose adaptation are achieved after 3 days. In patients with severe renal impairment or end-stage renal disease, a maximum dose of LCM of 300 mg should not be exceeded. Hemodialysis significantly decreases systemic LCM exposure, by approximately 57% [Doty *et al.* 2013]. LCM dosage supplementation up to 50% of the divided daily dose should be considered directly after the end of hemodialysis. Also in patients with mild or moderate hepatic impairment a maximum dose of 300 mg/day should not be exceeded [Doty *et al.* 2013]. LCM exhibits low potential for clinically-relevant pharmacokinetic drug–drug interactions with AEDs as well as other common medications [Cawello *et al.* 2010, 2012, 2013; Stockis *et al.* 2013; Cawello *et al.* 2014a, 2014b; Cawello, 2015].

Clinical efficacy

Overview of double-blind randomized placebo-controlled trials

Results from three double-blind randomized controlled trials (RCTs) led to the approval of LCM as adjunctive treatment for partial-onset seizures in Europe and in the USA in 2008. These trials (referred to as 'LCM-RCTs' below) consist of:

– SP667 [Ben-Menachem *et al.* 2007]: a phase IIb study including 418 patients in the USA and Europe. The study was designed to compare placebo *versus* LCM at doses of 200 mg/day, 400 mg/day and 600 mg/day, respectively; the related long-term extension study was SP615 [Rosenfeld *et al.* 2014].

– SP754 [Chung *et al.* 2010b]: a phase III study including 405 patients in the USA and comparing placebo *versus* LCM doses of 400 mg/day and 600 mg/day, respectively; the related long-term extension study was SP756 [Husain *et al.* 2012].

– SP755 [Halasz *et al.* 2009]: a phase III study including 485 patients in Europe and Australia was designed to compare placebo *versus* LCM doses of 200 mg/day and 400 mg/day, respectively; the related long-term extension study was SP774 [Rosenow *et al.* 2015].

Of about 1300 adult patients included in these three trials, 947 patients received LCM. There are several retrospective and prospective open-label studies of LCM treatment of children with epilepsy [Grosso *et al.* 2014b; Pasha *et al.* 2014; Yorns *et al.* 2014]; however, no children took part in any of the LCM-RCTs.

Efficacy data from RCTs

The efficacy data from LCM-RCTs are summarized in Table 1. LCM was effective in the reduction of the mean seizure frequency in doses of 400 mg/day and 600 mg/day. Median seizure reduction was also significant for 200 mg/day in SP755, but not in SP667. Furthermore, intake of 200 mg/day did not result in a significant increase of the 50% responder rate in either study, indicating the dose-dependency of LCM efficacy.

Based on analysis of covariance (ANCOVA) models, the mean seizure reduction over placebo in the intention-to-treat set was 14% (200 mg/day), 15–28% (400 mg/day), and 21–25% (600 mg/day), respectively. In the per-protocol set (PPS), mean seizure reduction over placebo was consistently higher (200 mg/day: 22–35%; 400 mg/day: 21–45%, 600 mg/day: 32%).

Pooled analyses

Data from SP667, SP754 and SP755 are the basis for several pooled analyses. A Cochrane review [Weston *et al.* 2015] rated the three RCTs as adequate in terms of methodology and low risk for

Table 1. Efficacy data from phase II and phase III studies [Ben-Menachem *et al.* 2007; Halasz *et al.* 2009; Chung *et al.* 2010b] ITT population, ranges (min–max).

Reference	Study no.	Phase	Design	Study population, years	Study duration, weeks	Median seizure reduction, %	50% responder rate, %	Seizure freedom, %
Ben-Menachem *et al.* [2007]	SP667	IIb	r, db, pc	418 (18–65)	28 (8 b + 6 ti + 12 m + 2 tr)	placebo: 10	placebo: 21.9	placebo: 0
						200 mg: 26 ($p = 0.1010$)	200 mg: 32.7 ($p = 0.0899$)	200 mg: 0.9
						400 mg: 39 ($p = 0.0023$)	**400 mg: 41.1 ($p = 0.0038$)**	400 mg: 4.6
						600 mg: 40 ($p = 0.0084$)	**600 mg: 38.1 ($p = 0.0141$)**	600 mg: 0.9
Chung *et al.* [2010b]	SP754	III	r, db, pc	405 (16–70)	28 (8 b + 6 ti + 12 m + 2 tr)	placebo: 20.8	placebo: 18.3	placebo: 0
						400 mg: 37.3 ($p = 0.008$)	**400 mg: 38.3 ($p < 0.001$)**	400 mg: 2.5
						600 mg: 37.8 ($p = 0.006$)	**600 mg: 41.2 ($p < 0.001$)**	600 mg: 8.1
Halasz *et al.* [2009]	SP755	III	r, db, pc	485 (16–70)	26 (8 b + 4 t + 12 m + 2 ti)	placebo: 20.5	placebo: 25.8	placebo: 2.1
						200 mg: 35.3 ($p = 0.02$)	200 mg: 35.0 ($p = 0.07$)	200 mg: 3.6
						400 mg: 36.4 ($p = 0.03$)	**400 mg: 40.5 ($p = 0.01$)**	400 mg: 2.4

Statistically significant results are shown in **bold.**
b, baseline period; db, double blind; ITT, intention-to-treat; m, maintenance period; pc, placebo-controlled; r, randomized; ti, titration period; tr, transition period.

Table 2. Frequent and dose-dependent treatment-emergent adverse events (TEAEs). Frequency ranges min–max in % from LCM-RTCs [Ben-Menachem *et al.* 2007; Halasz *et al.* 2009; Chung *et al.* 2010b].

		placebo	200 mg/day	400 mg/day	600 mg/day	LCM total
TEAE	Dizziness	5–11	10–24	16–42	51–55	13–45
	Abnormal/blurred vision	3–5	4	11	16–20	12–13
	Ataxia/abnormal coordination	1–3	4	6–13	11–23	5–13
	Diplopia	1–3	4–8	10–11	14–19	9–13
	Nausea	1–9	6–10	8–15	17–18	7–14
	Fatigue	4–5	5–10	6–12	20	6–14
	Nystagmus	5	3	5–8	10	6–9
	Vomiting	2–3	3–10	6–12	12–20	4–12
	Tremor	8	-	9	14	11
Study discontinuation due to TEAE		5	6–11	15–19	30	11–20
Serious TEAE		3–5	8–9	6–9	3	6–9

LCM, lacosamide; RTC, randomized controlled trial; TEAE, treatment-emergent adverse event.

systematic bias, resulting in a high quality of evidence for 50% responder and withdrawal rates. Quality of evidence for seizure freedom was rated as moderate due to the small number of events. Risk ratios (RRs) for ⩾50% seizure reduction as compared with placebo were calculated as 1.7 [95% confidence interval (CI), 1.38–2.10] for all doses of LCM, while the RR for seizure freedom was 2.5 (95% CI, 0.85–7.34).

Median seizure reduction rates of 18% (placebo), 33% (LCM 200 mg/day; $p < 0.01$ compared with placebo) and 37% (LCM 400 mg/day; $p < 0.001$) were calculated [Beydoun *et al.* 2009]. Likewise, 50% responder rates calculated from the pooled data were significant in comparison with placebo (23%) for LCM 200 mg/day (34%; $p < 0.05$) and for LCM 400 mg/day (40%; $p < 0.001$).

Valuable *post hoc* analyses were performed by [Chung *et al.* 2010a]. Examining the onset of LCM efficacy, they found a significant difference in the median reduction of seizure frequency for LCM 100 mg/day *versus* placebo during the first week (33% *versus* 19%) and during the second week (34% *versus* 20%). Neither prior epilepsy surgery nor implantation of a vagus nerve stimulator was associated with efficacy differences. Also, there were no apparent differences in LCM efficacy between patients with different concomitant anticonvulsant drugs. Another *post hoc* analysis [Sake *et al.* 2010] confirmed the efficacy of add-on LCM in patients who were on a traditional sodium channel blocker (phenytoin, carbamazepine, oxcarbazepine, lamotrigine). Efficacy was higher in patients on non-sodium channel blockers with median seizure reduction of 38% (200 mg/day), 63% (400 mg/day) and 79% (600 mg/day) *versus* placebo (28%), but a direct comparison was not possible with the LCM-RCT database.

A meta-analysis that included all available RCT data of 'new' anticonvulsants (oxcarbazepine, lamotrigine, topiramate, gabapentin, pregabalin, levetiracetam, tiagabine, zonisamide, eslicarbazepine and LCM) confirmed efficacy of LCM over placebo but estimated a lower efficacy of LCM compared with the pooled efficacy of the other new anticonvulsants [Costa *et al.* 2011]. Because the differences disappeared after adjustment for the percentage of responders in the placebo group, this finding was attributed to the relatively high rate of seizure reduction in the placebo groups of the LCM-RCTs, which in turn may have been influenced by study location and year.

Safety and tolerability

Safety and tolerability data from RCTs

The safety and tolerability data from SP667, SP754 and SP755 are summarized in Table 2. Overall, LCM tolerability was dose-dependent. Doses of 200 mg/day and 400 mg/day were fairly well tolerated, while treatment discontinuation increased to 30% in the 600 mg/day group.

Treatment-emergent adverse events (TEAEs) were usually of mild or moderate intensity. The most frequent and dose-dependent TEAEs (i.e. likely to be treatment related) were dizziness, abnormal vision, diplopia, nystagmus, fatigue, tremor, ataxia and other coordination abnormalities as well as nausea and vomiting. Another frequently reported TEAE was headache; however, frequency was not dose-related, and headache did not consistently appear more often in LCM-treated patients than in the placebo group. An additional seven RCTs conducted for other indications (diabetic neuropathic pain, migraine, fibromyalgia, knee osteoarthritis) [Zaccara *et al.* 2013] and one RCT that assessed cardiac side effects of LCM in healthy volunteers [Kropeit *et al.* 2015] reported very similar TEAE profiles in clinically different populations.

Serious adverse events (SAEs) were rare and comprised seizures, dizziness, nausea, vomiting, nystagmus, and psychiatric disorders. Overall, one patient died during the course of one of the LCM-RCTs. This patient, who was randomized to LCM 200 mg/day treatment, committed suicide. The death was considered to be unrelated to the trial medication [Biton *et al.* 2015].

Cardiac safety

Because LCM acts on VGSC, treatment-induced atrioventricular (AV) block is a possible concern. In SP667, SP754 and SP755, the PR interval increased in a dose-dependent manner (400 mg/day, 4.2–4.6 ms; 600 mg/day, 6.1 ms). This elevation remained clinically silent. A pooled analysis [Rudd *et al.* 2015] confirmed these findings: mean changes in PR interval from baseline to the end-of-maintenance period were −0.3 ms (placebo), 1.4 ms (LCM 200 mg/day), 4.4 ms (LCM 400 mg/day) and 6.6 ms (LCM 600 mg/day). The frequency of first-degree AV block differed between SP667 (placebo, 3.2%; LCM 200 mg/day, 4.7%; LCM 400 mg/day, 4.9%; LCM 600 mg/day, 4.9%) and SP754/755 (placebo: 2.4%; LCM 200 mg/day, 1.3%; LCM 400 mg/day, 2.3%; LCM 600 mg/day, 1.1%). The reason for this discrepancy remains unexplained, the more so as a higher threshold was defined for AV block in SP667 (220 ms) than in SP754/755 (209 ms). Patients with AV block were allowed to continue the study and apparently did not experience clinical side effects from the prolonged conduction time. No instance of second- or third-degree AV block was reported. Monitoring of electrocardiograms (ECGs) might be considered in patients with known conduction problems and in those treated by PR interval-prolonging drugs such as carbamazepine, lamotrigine, and pregabalin.

QTc intervals were not affected. A randomized, double-blind, positive- and placebo-controlled trial (SP640) was conducted in healthy volunteers to determine the effects of LCM (400 and 800 mg/day) on repolarization and AV conduction [Kropeit *et al.* 2015]. Moxifloxacin, which prolongs the QT interval, was used as a positive control. This trial confirmed the findings of the LCM-RCTs: QTc intervals remained unaffected, while LCM treatment led to a dose-dependent increase in PR intervals (400 mg/day: 7.3 ms over placebo; 800 mg/day: 11.9 ms over placebo). The cardiac-related TEAEs reported were palpitations (placebo, 3.2%; LCM 400 mg/day, 3.3%; LCM 800 mg/day, 4.2%) and sinus tachycardia (LCM 800 mg/day, 1.4%). Altogether clinical practice shows a good cardiac tolerability of LCM.

Pooled analyses

Combined evaluation of safety data from the three LCM-RTCs revealed similar results to those obtained for the single studies [Beydoun *et al.* 2009; Biton *et al.* 2015; Weston *et al.* 2015]. The RR for treatment withdrawal in LCM-treated patients as compared with placebo was 1.9 for all doses [Weston *et al.* 2015]. Abnormal coordination (RR 6.1), diplopia (RR 5.3), dizziness (RR 3.5) nausea (RR 2.4) and vomiting (RR 3.5) were significantly associated with LCM intake, while headache (RR 1.3), fatigue (RR 3.5), nystagmus (RR 1.5) and somnolence (RR 1.4) were not.

A thorough pooled safety and tolerability analysis was performed by [Biton *et al.* 2015]. In general, the incidence of TEAEs was higher during the titration phase than during the maintenance phase. Rare TEAEs observed included rash (incidence, 2.9% in the LCM group *versus* 3.0% in the placebo group), weight gain (1.2% *versus* 0.5%), weight loss (1.1% *versus* 0.8%), increased alanine aminotransferase (ALAT) levels ⩾3 times the upper limit of normal (0.5% *versus* 0%), psychosis (0.3% *versus* 0%) and depression (2.1% *versus* 0.5%).

LCM tolerability seemed lower when the drug was combined with ‘traditional’ sodium channel blockers, such as carbamazepine, oxcarbazepine, lamotrigine and phenytoin [Sake *et al.* 2010].

Regarding LCM influence on mood and anxiety, one study [Moseley *et al.* 2015] showed significant decrease in depressive symptoms in patients on LCM. Overall, NDDI-E and GAD-7 scores prior and after initiation of LCM were not significantly affected by a history of mood disorders, concomitant psychiatric medications, or concomitant AEDs with mood-stabilizing effects [Moseley *et al.* 2015].

Post-marketing surveillance

Further information on the efficacy and tolerability of LCM as an adjunctive AED can be drawn from mono- and multicenter reports on the use of LCM in daily practice. For details regarding efficacy, please refer to Table 3. A multitude of clinical trials with a prospective or descriptive study design and a total number of more than 1500 enrolled patients showed a >50% reduction in seizure frequency in 23–48.2% of patients [Wehner *et al.* 2009; Garcia-Morales *et al.* 2011; Stephen *et al.* 2011; Husain *et al.* 2012; Miro *et al.* 2013; Novy *et al.* 2013; Verrotti *et al.* 2013; Villanueva *et al.* 2013; Legros *et al.* 2014; Borzi *et al.* 2016; Lang *et al.* 2016]. Seizure freedom under adjunctive therapy with LCM of up to 33% and a reduction of seizure frequency >90% in approximately 26% has been shown [Harden *et al.* 2012; Steinhoff *et al.* 2016]. In addition, several retrospective, descriptive or comparative trials confirmed these results, reporting a reduction in seizure frequency of >50% in up to 69% and an overall seizure freedom of up to 33% under treatment with LCM [Flores *et al.* 2012; Harden *et al.* 2012; Kamel *et al.* 2013; Villanueva *et al.* 2013]. In addition to its efficacy in adults, LCM has been shown to achieve a >50% responder rate in 33.3% of children suffering from generalized seizures (n = 19) and 36.8% of pediatric patients with focal seizures (n = 12, mean age 10.8 years) [Verrotti *et al.* 2013]. Aside from oral application, adjunctive intravenous administration of LCM (n = 130, mean dosage 300 mg/day, mean duration of treatment 2d) in adults and children suffering from generalized and focal seizures was recently shown to be highly effective and well tolerated in a multicenter noninterventional study [Lang *et al.* 2016].

Moreover, several case reports have proven the efficacy of adjunctive LCM treatment in various epilepsy syndromes or chronic diseases accompanied by epileptic seizures, such as post-hypoxic myoclonus syndrome (Lance–Adams syndrome) [Galldiks *et al.* 2010] and Lennox–Gastaut syndrome (LGS). Regarding the efficiency of LCM in LGS, contradictory reports have been published. In a multicenter retrospective open-label treatment study of children suffering from LGS (n = 18, mean age 12.3 years), a responder rate of 33% was reported [Grosso *et al.* 2014a]. Conversely, several case reports have shown an increase in seizure frequency in LGS [Cuzzola *et al.* 2010; Andrade-Machado *et al.* 2012, 2015]. One case report showed *de novo* continuous epileptic negative myoclonus triggered by the addition of LCM to carbamazepine, that promptly reverted after carbamazepine dosage reduction [Belcastro *et al.* 2011]. These discrepancies show the difficulty of an anticonvulsive treatment of LGS but prove LCM to be an alternative AED in the therapy of LGS.

Aside from its robust efficacy, LCM has also proven acceptable in terms of its tolerability and side-effect profile. In summary, the most common reported adverse effects (AEs) in post-marketing studies were similar to those reported in the RCTs. These included sedation, somnolence, fatigue, dizziness, nausea, unsteadiness, ataxia, headache and double vision [Flores *et al.* 2012; Husain *et al.* 2012; Kamel *et al.* 2013; Novy *et al.* 2013; Verrotti *et al.* 2013; Villanueva *et al.* 2013; Steinhoff *et al.* 2016]. For details on common AEs, please refer to Table 4. Several case reports have documented life-threatening AEs, such as higher-degree AV blockage, atrial flutter/fibrillation and sinus node dysfunction [Degiorgio, 2010; Nizam *et al.* 2011; Chatzistefanidis *et al.* 2013; Chinnasami *et al.* 2013; Degiorgio *et al.* 2013]. Another case report showed reversible suicidal ideation after several months of exposure to 400 mg/day LCM in a 47-year-old man suffering from partial epilepsy since adolescence [Kellinghaus, 2013]. In a report of an attempted suicide with 12 g of LCM, a transient increase in PR interval was shown, while complete physical recovery occurred after several days of supportive treatment [Bauer *et al.* 2010]. A recent international noninterventional multicenter study focused on the safety and tolerability of LCM in patients with uncontrolled partial-onset seizures. The study's findings revealed an incidence of cardiovascular TEAEs in the LCM-treated cohort of 0.8% (n = 487, <65 years), which is comparable with the incidence observed in the cohort treated with other AEDs (0.9%, n = 448, <65 years) [Steinhoff *et al.* 2016]. Likewise, the incidence of psychological TEAEs, such as depression or sui-

Table 3. Efficacy data from post-marketing studies (ranges min–max).

Reference	Design	*n*	Patient characteristics	Study population seizure types	LCM regimen	Outcome
Wehner *et al.* [2009]	Prospective, descriptive, Germany	25 Discontinuation: 7 (28%), 3 due to TEAEs, 1 due to death from cancer, others unknown	Adolescents, adults Female: 13 Male: 12 Mean age: 43 years (16–73)	Refractory focal epilepsy	Initial: 50 mg orally twice daily Target dose: 400 mg/day Titration: 50 mg weekly Follow up: 6 months	32%: ⩾ 50% reduction in seizure frequency 12%: ⩾90 % reduction in seizure frequency
Garcia-Morales *et al.* [2011]	Prospective, descriptive, Spain	60 Discontinuation 8 (13.3%), 6 due to TEAEs, 2 due to increase seizure frequency	Adults Female: 32 Male: 28 Mean age: 37 years (21–69)	Refractory focal epilepsy	Initial: 50 mg orally once daily Target dose: 200–500 mg/day Titration: 50 mg weekly Follow up: 13–24 months	47%: ⩾50% reduction in seizure frequency 3.3%: seizure-free
Stephen *et al.* [2011]	Prospective, descriptive, Scotland	113 Discontinuation: 14 (12.4%), 10 due to TEAEs, 4 due to lack of efficacy	Adults Female: 56 Male: 57 Median age: 39 years (18–74)	Refractory focal epilepsy	Initial: 50 mg orally once daily for 2 weeks Target dose: 200–4 mg/day Titration: unexplained	Analyzed for 65 patients: 24.6%: ⩾ 50% reduction in seizure frequency 26.2%: seizure-free for ⩾ 6 months
Husain *et al.* [2012] SP756	Prospective, descriptive, USA	308 Discontinuation: 170 (55.2%), 35 due to TEAEs, 80 due to lack of efficacy, 16 due to patient withdrawing consent, 1 due to protocol deviation, 11 due to unsatisfactory compliance, 8 lost to follow up. Other: 19 (6.2%)	Female: 146 Male: 162 Mean age: 38.2 years	Refractory focal epilepsy	Initial: 200 mg orally/day Titration: Decrease to 100 mg/day, or increase to 800 mg/day (100 mg/day weekly)	307 patients analyzed: 48.5%: ⩾ 50 % reduction in seizure frequency
Villanueva *et al.* [2012]	Prospective, descriptive cohort study, Spain	158 Discontinuation: 48 (30%), 30 due to TEAEs, others due to lack of efficacy or unspecified	Adolescents, adults Female: 76 Male: 82 Mean age: 42.1 years (12–83)	Focal epilepsy (93.7% refractory)	Initial: 50 mg once daily or twice daily Target dose: 400 mg/day Titration: 50 mg once or twice/day weekly follow up: 12 months	47%: ⩾50% reduction in seizure frequency 12%: Seizure-free at 12-months follow up

(Continued)

Table 3. (Continued)

Reference	Design	*n*	Patient characteristics	Study population seizure types	LCM regimen	Outcome
Verrotti *et al.* [2013]	Prospective, descriptive, Italy	118 Discontinuation Group A: 22% Group B: 40.7% due to lack of efficacy (6.8% group A; 23.7% group B) due to an increase in seizure frequency (11.9% group A; 8.5% group B) because of AEs (3.4% group A; 8.5% group B)	Group A: Mean age 18.8 years (4–15) Female: 29 Male: 30 Group B: Mean age: 21 years (16–38) Female: 25 Male: 34	Group A: Generalized seizures: 12 (20.3%) Focal seizures: 19 (32.3%) Focal evolving to bilateral seizures: 7 (11.9%) Mixed seizures: 21 (35.6%) Group B: Generalized seizures: 4 (6.8%) Focal seizures: 10 (16.9%) Focal evolving to bilateral seizures: 8 (13.6%) Mixed seizures: 37 (62.7%)	Group A Initial: 1 mg/kg/day Target dose: 3– 12 mg/kg/day Titration: 1 mg/kg/day weekly Group B: Initial: 100 mg daily Target dose: 100–600 mg daily Titration: 50 mg/day weekly Follow up: 3, 6 and 12 months	12-months follow up: Group A ($n = 11$): 52.4 %: ⩾50% reduction in seizure frequency Group B ($n = 14$): 37.8%: ⩾50% reduction in seizure frequency
Novy *et al.* [2013]	Prospective, descriptive, UK	376 Discontinuation: 206 (54.8%), 78 due to TEAEs 127 due to lack of efficacy or increased seizure frequency	Adolescents, adults Female: 212 Male: 164 Median age: 39.6 years (17–76)	Refractory focal epilepsy: 91.2% Refractory generalized epilepsy: 3.7% Unclassified: 5.1%	Initial: 0.8%: <50 mg/day 91%: 50 mg/day 8.2%: 50–100 mg/day Median dose: 300 mg/day (25–700 mg/day) Titration: not described Median duration: 1.6 years	18%: ⩾ 50% reduction of seizure frequency 1.2%: seizure-free after 12 months
Flores *et al.* [2012]	Retrospective, descriptive, UK	403 Discontinuation:150 (38%), 84 due to TEAEs, 35 due to lack of efficacy, 20 due to increase of seizure frequency, 11 unknown	Adolescents, adults Female: 204 Male: 199 18.1% with learning disabilities Mean age: 42 years (17–82)	Focal epilepsy (92.3%) Generalized epilepsy (5%) Unclassified (2.7%)	Initial: 25–200 mg/day Mean max. dose: 279.4 (25–700) mg Mean follow up: 11.6 months	285 patients analyzed > 6 months follow up: 35.7%: ⩾ 50% reduction in seizure frequency 9.8%: seizure-free 21.7%: ⩽ 50 reduction of seizure frequency 18.6%: increase of seizure frequency 23.8%: no response
Harden *et al.* [2012]	Retrospective, descriptive, USA	67 Discontinuation: 14 (21%), 5 due to TEAEs, 4 due to lack of efficacy, 5 for both	Adults Female: 35 Male: 32 Mean age: 38 year (18–82)	Complex partial seizures, 61 (91%) Generalized tonic-clonic seizures, 24 (36%) Atonic seizures 11 (16%)	Mean dose: 278 mg/day (50–600 mg/day) Mean duration: 7 months (1–12 months)	69%: ⩾ 50% reduction in seizure frequency 33%: seizure-free

Table 3. (Continued)

Reference	Design	*n*	Patient characteristics	Study population seizure types	LCM regimen	Outcome
Kamel *et al.* [2013]	Retrospective, descriptive, Australia	128 Discontinuation: 24 (19%) not further specified	Adults Female: 64 Male: 64 Mean age: 29 years (18–72)	Focal epilepsy: 93% Generalized epilepsy: 7%	Initial: 50 mg twice daily Final mean dose: 250 mg/day (100–500) Titration: not described Mean duration: 7 months (1–17 months)	41%: ⩾ 50% reduction in seizure frequency 11%: seizure-free
Villanueva *et al.* [2013]	Retrospective, descriptive, Spain	500	Adults Mean age: 42 years (18–88) Male: 268 patients (53.6%) Female: 232 patients (46.4%)	Focal epilepsy	Initial dose/titration: (1) initial: 100 mg/day titration: 100 mg/day/week (18%) (2) initial: 50 mg/day titration: 50 mg/day/week (35%) (3) initial: 50 mg/day titration: 50 mg/day/ every 10 days (13%) (4) initial: 50 mg/day titration: 50 mg/day every 2 weeks (18%) (5) other initial dose and titration (2%) Missing: 14% Maintenance: mean 339 mg/day Follow up and retention rate: at 3 (97%), 6 (90%) and 12 (84%) months	3 months: seizure-free: 16%, >50% seizure frequency reduction 44% 6 months: seizure-free 16%, >50% seizure frequency reduction 53% 12 months: seizure-free: 15%, >50% seizure frequency reduction 57.1% Overall seizure reduction rate: not reported
Nizam *et al.* [2011]	Retrospective, descriptive, USA	1	Male Age: 45	Frontal lobe epilepsy with generalized tonic-clonic seizures	Initial: not described Maintenance dose: 200 mg/day	Seizure-free for one year, LCM replacing zonisamide since 3 months, then seizure recurrent one week prior to hospitalization
Degiorgio *et al.* [2013]	Retrospective, descriptive, USA	1	Male: Age: 49 no prior history of cardiac events	Frontal lobe epilepsy with complex partial and generalized tonic-clonic seizures	Initial: not described Maintenance dose: severe ventricular tachycardia After hospitalization: lowered dose by 100 mg/day until termination.	Intractable

(Continued)

Table 3. (Continued)

Reference	Design	*n*	Patient characteristics	Study population seizure types	LCM regimen	Outcome
Grosso *et al.* [2014a]	Retrospective, descriptive, Italy	18	Children mean age: 12 (4–15) years Male: 12 patients (67%) Female: 6 patients (33%)	LGS: 18 (100%) Tonic seizures: 14 (78%) Atypical absences: 12 (67%) Drop-attacks: 10 (55%) Myoclonic seizures: 6 (33%) Tonic-clonic seizures: 6 (33%) Focal seizures: 5 (28%)	Titration: 1–2 mg/kg, increased every 7–10 days Maintenance: mean 15 (10–18) mg/kg/day Follow up: every 2–3 months, mean period of LCM treatment 9 (3–17) months	Overall Seizure reduction rate: 30% Seizure-free: 0% >50% seizure frequency reduction: 6 (33%) Increased: 3 (17%) Tonic seizure frequency: >50% seizure frequency Reduction: 4 (28%) Increased: 2 (14%) Drop-attacks frequency: >50% seizure frequency reduction: 3 (30%) Increased: 2 (20%) Tonic-clonic seizure frequency: >50% seizure frequency reduction: 2 (33%) Increased: 2 (33%) Atypical absences/ myoclonic seizures: data not provided
Andrade-Machado *et al.* [2015]	Retrospective, descriptive, Colombia	19	Adults Mean age: 27 (18–61) years Male: 12 patients (63%) Female: 7 patients (37%)	LGS: 19 (100%) Tonic seizures: 19 (100%) Atonic seizures: 16 (84%) Astatic seizures: 18 (95%) Tonic-clonic seizures: 15 (79%) Focal seizures: 3 (16%)	Initial dose: median 25 (25–50) mg/day, increased every 2 weeks Maintenance dose: median 200 (50–300) mg/day Follow up: 18 months	Overall Seizure-free: 0% >50% seizure frequency reduction: 2 (11%) Tonic seizure frequency: >50% seizure frequency reduction: 1 (5%) Increased: 16 (78.9%) Astatic seizure frequency: >50% seizure frequency reduction: 0 (0%) Increased: 7 (39%) Tonic-clonic seizure frequency: >50% seizure frequency reduction: 11 (73%) Increased: 0 (0%) Focal seizure frequency: >50% seizure frequency reduction: 3 (100%) Increased: 0 (0%) Overall seizure reduction rate: not reported

Table 3. (Continued)

Reference	Design	*n*	Patient characteristics	Study population seizure types	LCM regimen	Outcome
Steinhoff *et al.* [2016]	Cohort study, Germany	1005 (511 adjunctive LCM treatment, 493 another AED treatment) Discontinuation of LCM cohort: 255 (49.9%) Due to: AE: 100 (19.6%) Lack of efficacy: 70 (13.7%) Lost to follow up: 46 (9.0%) Withdrawn consent: 16 (3.1%) Other: 23 (4.5%)	Adults For LCM group: Female: 266 Male: 245 Mean age: 39.8 ± 13.58	Uncontrolled partial-onset seizures	Modal dose over the treatment: 200 mg/day (50 mg/day–700 mg/day) At 12 months: 400 mg/day	Seizure freedom: up to 33% reduction of seizure frequency >90%: approximately 26%
Lang *et al.* [2016]	Prospective, descriptive, Germany	130 Reasons for LCM IV: Preparation of surgery 30 (25.2%), Convulsive SE 29 (24.4%), Nonconvulsive SE 22 (18.5%), Series of seizures 19 (16.0%), Gastrointestinal problems 7 (5.9%), Acute seizure 5 (4.2%), Coma 1 (0.8%), Others 17 (14.3%)	Adults Children Female: 63 (52.9%), Male: 56 (47.1%), Mean age: 59.1 (1–92.2) years	Focal 76 (63.9%), Generalized 20 (16.8%), Not classifiable 19 (16.0%), Missing 4 (3.4%)	LCM IV Initial: 50 mg twice a day Titration: 100 mg twice a day after one week Target dose: 200 mg twice a day	SE or series of seizure: In 45 (70.3%) of 64 patient's seizure activity ceased in close temporal relation to administration of LCM IV. Investigators rated the efficacy of LCM IV as good or very good for the majority of patients (77.6%)
Borzi *et al.* [2016]	Prospective, descriptive, Italy	100 Adults Discontinuation: 14 due to other findings in MRI than hippocampal sclerosis	Cohort of 86: Female: 50 Male: 36 Mean age: 43.4 ± 12.53 year	Nonlesional TLE and TLE with hippocampal sclerosis	Initial: 50 mg/day Titration: 50 mg weekly Target dose: 200–400 mg/day Median follow up: 18 months	Responder: 52.3% >50% reduction of seizure frequency: 73.3% Seizure-free: 26.6 %

AE, adverse event; AED, antiepileptic drug; IV, intravenous; LCM, lacosamide; LGS, Lennox–Gastaut syndrome; MRI, magnetic resonance imaging; SE, status epilepticus; TEAE, treatment-emergent adverse event; TLE, temporal lobe epilepsy.

Table 4. Common AEs from post-marketing studies (studies including more than 100 patients were included).

Reference	Consciousness cognitive	CNS	Vegetative	Psychobehavioral	Other	Total, %
Husain *et al.* [2012]	Fatigue (11.7%)	Nystagmus (11.0%), Dizziness (50.0%), Convulsion (17.2%), Diplopia (15.3%), Balance disorder (13.3%), Tremor (13.2%)	Vomiting (15.9%)	Depression (11.7%)	Contusion (18.5%), Nasopharyngitis (17.2), Fall (15.9%), Respiratory tract infection (13.0%), Skin laceration (12.7%), Back pain (11.0%), Sinusitis (10.4%)	93.5
Villanueva *et al.* [2012]	Drowsiness (10.1%)	Dizziness (25.3%), Ataxia (9.5%), Blurred vision/diplopia (3.8%), Language disturbances (1.2%)		Irritability (7.0%)	Skin reaction (2.5%), Headache (1.9%), Body weight increase (1.2%)	49.4
Novy *et al.* [2013]	Drowsiness (13.6%), Tiredness (4.0%), Cognitive complaints (3.5%) Insomnia (1.6%)	Dizziness (25.8%), Double/blurred vision (19.4%), Dysarthria (1.3%)	Nausea (5.1%)	Mood disorders (2.9%), Irritability (1.6%), Anxiety (1.1%)	Headache (4.0%), Allergic (1.9%), Others (8.0%)	61.4
Flores *et al.* [2012]	Sedation/somnolence (22.1%) Confusion/mental slow (1.6%) Sleep disturbances (1.3%) Memory problems (1.1%)	Dizziness (18.2%) Unsteadiness (11.4%) Double/blurred vision (11.2%) Slurred speech (1.3%) Numb fingers (1.1%)	Nausea/GI disturbances (14.9%)	Mood change (1.6%) Hallucinations (1.3%)	Headache (8.5%) Skin irritation (3.5%) Weight gain (1.9%)	40
Kamel *et al.* [2013]	Sedation (14%)	Dizziness (20%), Blurred vision (5%)		Depression (3%)	GI upset (4%), Headache (3%), Facial swelling (2%), Weight loss (2%), Rash (2%)	–
Villanueva *et al.* [2013]	Drowsiness (12%), Mental/memory slowness (2%)	Dizziness (20%), Blurred vision (7%), Ataxia (6%) Tremor (1%)		Irritability (3%)	Headache (4%), GI disturbance (2%), Skin reaction (1%), Other (4%)	40
Steinhoff *et al.* [2016]	Fatigue (15.9%), Memory impairment (2.2%), Disturbance in attention (1.4%), Cognitive disorder (1.0%)	Dizziness (21.7%), Diplopia (10.6%), Vertigo (8.8%), Convulsion (7.0%)	Nausea (9.6%)	Depression (2.9%)	Headache (11.0%)	73.8
Verrotti *et al.* [2013]	Somnolence (4.3%)	Dizziness (8.6%), Diplopia (1.7%), Paresthesia (1.7%)	Vomiting (4.3%), Dyspepsia (4.3%), Nausea (3.4%), Lack of appetite (1.7%)	Irritability (3.4%)	Headache (5.9%)	29.7

GI, gastrointestinal; CNS, central nervous system.

Table 5. Safety and efficacy data from studies on LCM in SE.

Reference	Design	*n*	Patient characteristics	Study population seizure types	LCM regimen	LCM dosing (mg)	Outcome	AEs (*n* of patients)
Kellinghaus *et al.* [2011]	Retrospective, descriptive, Germany	39	Adults mean age: 63 (18–90) years Male: 18 patients (46%) Female: 21 patients (54%)	Convulsive generalized 6/39 (15%) Complex partial 17/39 (44%) Simple focal 16/39 (41%)	LCM 1st/2nd: 5/39 (13%) LCM 3rd: 19/39 (49%) LCM 4th or later: 15/39 (38%) latency to LCM onset (total, hour): mean: 116.5 (0.5–1440)	Bolus: 328 mg (200–400) 1st day: 424 mg (200–600)	Overall termination after LCM, no further AED: 44% <6 h after LCM IV, no other AED after LCM: 7/39, 18% >6 h after LCM IV no other AED after LCM 10/39, 26% success rate LCM first/second: 3/5 (60%) success rate LCM third 11/19 (58%) success rate LCM fourth or later 3/15 (20%)	Overall: 30 (77%) allergic skin reaction (1) (possible domperidone effect) sedation (25) (always after administration of benzodiazepines, barbiturates or propofol) Hypotension (4) (association with propofol or phenytoin) no ECG changes observed
Albers *et al.* [2011]	Retrospective, descriptive, Germany	7	Adults 33–83 years Male: 6 patients (86%) Female: 1 patient (14%)	Focal SE (7/7)	LCM median 4th AED (range 2–5)	Initial dose: 400 mg IV Maintenance: 400 mg/day IV	Response to LCM within 24 h: 100%	No side effects or interactions attributable to LCM
Goodwin *et al.* [2011]	Retrospective, descriptive, USA	9	Adults mean age: 63 (47–89) years Male: 2 patients (22%) Female: 7 patients (78%)	NCSE 6/9 (67%) CSE 3/9 (33%)	LCM median 3rd AED (range 2–5)	Initial dose: 200 mg IV Maintenance: 400 mg/day Follow up: 48 h prior to RSE onset to 7 days after initiation of LCM	No response to LCM (0/9), defined as absence of EEG seizure activity within 4 h or for 24 h following emergence from burst suppression	Overall: 2 (22%) Acute angioedema: 2 (22%)
Hofler *et al.* [2011]	Retrospective, descriptive, Austria	31	Adults median age: 62 (22–95) years Male: 17 patients (55%) Female: 14 patients (45%)	CSE 11/31 (36%) FSE 10/31 (32%) NCSE 10/31 (32%)	LCM 1st 7% (2/31); LCM 2nd 19% (6/31); LCM 3rd 48% (15/31); LCM 4th or later 26% (8/31)	Initial dose: median 200 (200–400) mg IV Maintenance: median 200 (0–400) mg/day IV Follow up: 24 h after IV LCM	Termination: SE overall: 25 (81%) CSE: 10/11 (91%) FSE: 8/10 (80%) NCSE: 7/10 (70%)	Not reported
Koubeissi *et al.* [2011]	Retrospective, descriptive, USA	4	Adults mean age: 66 (53–79) years Female: 4 Male: 0	NCSE	LCM median 4th AED (range 2–5)	Initial: 50–100 mg IV maintenance dose: 100–200 mg twice a day Interval from NCSE onset to LCM therapy: 3–50 h	Seizure cessation: 100% Time from begin of LCM therapy to seizure control: 15 min to 2 h	No AEs attributed to IV LCM, including allergic reactions, cardiac, or respiratory problems (0%)
Rantsch *et al.* [2011]	Retrospective, descriptive, Germany	9 (10 episodes)	Adults mean age: 67 (52–84) years Male: 3 patients Female: 6 patients	NCSE: 80% EPC: 20%	Median LCM as 6th drug (range 4–12)	Loading dose: 50–100 mg IV as a bolus or 50 mg IV twice a day	Seizure cessation in 2 of 10 episodes: 20%	No AEs detected. (0%)

(Continued)

Table 5. (Continued)

Reference	Design	*n*	Patient characteristics	Study population seizure types	LCM regimen	LCM dosing (mg)	Outcome	AEs (*n* of patients)
Cherry *et al.* [2012]	Retrospective, descriptive, USA	24 patients with SE and isolated seizures (10 patients with SE: 13 episodes)	Adults SE group: Mean age: 51 (24–80) years Male: 5 patients Female: 8 patients	SE group: NCSE 7/13 (54%) Focal motor with altered consciousness 4/13 (31%) Myoclonic 0 Generalized convulsive 2/13 (15%)	LCM median 3rd AED (range 1–7)	SE group: loading/initial dose: mean (range) 180.8 mg (100–400) Infusion rate: mean (range) 3.33 mg/min (1.67–6.67) maintenance dose: mean (range) 361.5 mg/day (300–400) Time from seizure onset to LCM initiation: mean (hour) 39.5 (6.5–74)	SE group: seizure cessation 5/13 (38%) mean time to outcome (hour) 11.2 (1.5–21) >50% Reduction in seizures 7/13 (54%) mean time to outcome (hour) 8 (2–17)	Overall: 4/13 (31%) Hypotension (decreased systolic BP > 20 mm compared with baseline in absence of other BP lowering drugs) 3/13 (23%) Hypersensitivity reaction (rash and angioedema): 0 Cardiac arrhythmia: 0 Creatinine > 2.0: 0 Elevated liver function tests (>2x baseline) 1 (4%)
Mnatsakanyan *et al.* [2012]	Retrospective, descriptive, USA	10	Age: 16–90 years Male: 4 patients (40%) Female: 6 patients (60%)	NCSE	Median as 4th AED (range 2–8)	Initial dose: median 200– 300 mg IV within 30 min Maintenance dose: 200–400 mg/day follow up: 1 week – 10 months	SE termination: 7 (70%)	Overall: 0
Jain and Harvey [2012]	Retrospective, descriptive	3	Children range 12–17 years	refractory tonic SE	LCM as 4th or later AED duration of SE prior to LCM: 8–29 h	LCM bolus doses (2–2.5 mg/kg; 50–200 mg in the 1st 2 h)	SE termination 3/3 (1 after second dose)	Oculogyric crisis on day 4 (1) chorea on day 5 (1)
Miro *et al.* [2013]	Prospective, descriptive, Spain	34	Adults Mean age: 60 (22–86) years Male: 18 patients (53%) Female: 16 patients (47%)	FMSE 28/34 (82%) NCSE 5/34 (15%) GCSE 1/34 (3%)	Median interval latency: 48 (1–250) h after SE therapy initiation	Initial dose: 100–400 mg IV bolus (I) 100 mg IV: 1 (3%) (II) 200 mg IV: 7 (21%) (III) 300 mg IV 9 (26%) (IV) 400 mg IV 17 (50%) Maintenance: mean 324 (100–600) mg orally or IV/day	SE termination = LCM efficacy overall: 22/34 (64.7%) LCM 3rd/4th 13/34 (72.2%) LCM 5th or later 9/34 (56.3%)	Overall: 2 (6%) Diplopia: 1 Confusion/nystagmus: 1
Sutter *et al.* [2013]	Retrospective, comparative cohort, Switzerland	111 (86 included in analysis)	LCM group: mean age: 65 ± 15 years Male: 20 patients (44%) Female: 25 patients (56%) non-LCM group: Mean age: 60 ± 17 years Male: 25 patients (61%) Female: 16 patients (39%)	LCM group: focal or absence SE 17 patients (38%) NCSE 27 (60%) GCSE 1 (2%) Non-LCM group: focal or absence SE 12 patients (29%) NCSE 25 (61%) GCSE 4 (10%)	Order in which IV LCM was administered: Started simultaneously with 2nd AED: 3 (7%) 3rd AED 22 (49%) 4th AED 14 (31%) 5th AED 3 (7%) 6th AED 3 (7%) LCM as an adjunctive AED on mean as 4th drug (range 2–6)	200 mg IV Renal dysfunction: dose reduction Obesity ($n = 1$): 600 mg IV	Duration of SE (mean ± SD): LCM: 87 ± 159, Non-LCM: 134 ± 189, Seizure control: LCM: 93%, Non-LCM: 85% Multivariable analysis (adjustment for age): Duration of SE (hour): OR: −35.9 95% CI: −111.2–39.4, $p = 0.346$ Seizure control OR: 2.40 95% CI: 0.6–10.5, $p = 0.246$ Death OR: 0.34 95% CI: 0.1–0.9, $p = 0.035$	Overall: 0

Table 5. (Continued)

Reference	Design	*n*	Patient characteristics	Study population seizure types	LCM regimen	LCM dosing (mg)	Outcome	AEs (*n* of patients)
Belcastro *et al.* [2013]	Prospective, descriptive, Italy	16	Adults 77 ± 7 years of age Male: 7 patients Female: 9 patients	Stroke Patients, NCSE (7 simple, 9 complex)	LCM as initial drug	IV LCM as initial treatment, loading dose of 400 mg over 30 min, mean maintenance dose of 400 mg per day	Seizure control 7/16 (44%)	No significant AEs
Santamarina *et al.* [2013]	Retrospective, descriptive	92 LCM group: *n* = 31 non-LCM group: *n* = 61	Adults LCM group: mean age 62 (21–85) years, Male: 17 patients (55%) Female: 14 patients (45%) Non- LCM group: mean age 63 (20–91) years, Male: 32 patients (42%) Female: 29 patients (48%)	LCM group: Generalized convulsive 4/31 (12.9 %) Nonconvulsive 10/31 (32.3 %) Motor focal or *epilepsia partialis continua* 17/31 (54.8 %) Non-LCM group: Generalized convulsive 15/61 (24.6 %) Nonconvulsive 13/61 (21 %) Motor focal or *epilepsia partialis continua* 33/61 (54.1 %)	LCM as 2nd/ 3rd option (*n* = 13) LCM as 4th/ 5th option (*n* = 18)	LCM as 2nd/ 3rd option Infusion rate (mg/ min, median) 26.7 (23–40) Maintenance dose (mg/day) 400 LCM as 4th/ 5th option Infusion rate (mg/ min, median) 31.7 (25–40) Maintenance dose (mg/day) 400	Duration of SE prior to LCM (hour, median) 30 (3–200) Time to response to LCM (hour, median) 20 (1–96) LCM as 2nd/ 3rd option Responder rate 11 (84.6 %) Time to response to LCM (hour) 10 (1–72) LCM as 4th/ 5th option Responder 10 (55.6 %) Time to response to LCM (hour) 48 (20–96)	Dizziness (2) PR interval prolongation without clear clinical symptoms (2)
Legros *et al.* [2014]	Prospective, descriptive, Belgium	25 200 mg: *n* = 11 400 mg: *n* = 14	Adults 200 mg: Median age 54 (36–74) years Male: 7 patients (64%) Female: 4 patients (36%) 400 mg: Median age 60 (17–84) years Male: 6 patients (43%) Female: 8 patients (57%)	RSE (84%) SC (16%) Convulsive/ nonconvulsive/ generalized/ partial	Mean number of AEDs failed before LCM: 3 (range 2–5 200 mg group, 1–5 400 mg group)	Initial dose: (I) 200 mg IV over 15 min. (II) 400 mg IV over 15 min. Maintenance: 400 mg/day orally Follow up: after administration, 3 h and 24 h	Response to LCM Overall: 9 (36%) 200 mg: 2 (18%) 400 mg: 7 (50%) ($p = 0.2$) Early response (⩽ 3 h) to LCM 200 mg: 0 (0%) 400 mg: 4 (29%) ($p = 0.023$)	Overall: 5 (20%) Myoclonus/confusion: 1 Increased seizure severity: 1 Dizziness: 1 Ataxia: 1 Increased liver enzyme: 1

(Continued)

Table 5. (Continued)

Reference	Design	*n*	Patient characteristics	Study population seizure types	LCM regimen	LCM dosing (mg)	Outcome	AEs (*n* of patients)
Kellinghaus *et al.* [2014]	Retrospective, comparative cohort, Germany	46	Adults Median age: 68 (18–90) years Male: 23 patients (50%) Female: 23 patients (50%)	Focal SE: 19/46 (41%) NCSE: 15/46 (34%) GCSE: 12/46 (26%)	3rd AED overall: 46 3rd AED = LCM: 21 3rd AED = PHT: 15	Median interval latency from SE onset to therapy: 0.75 (0.2 –336) hour median 3rd AED dose: LCM: 400 (200–800) mg IV *versus* PHT: 1500 (750 – 1500) mg	SE termination after 3rd AED treatment: LCM 7/21 (33%) PHT 6/15 (40%) ($p = 0.68$) Median time to seizure termination: LCM 9.5 (0.5–240) h PHT 13.5 (0.5–28.5) h ($p = 0.48$)	Overall: LCM: 0/21 PHT: 4/15
Garces *et al.* [2014]	Retrospective, descriptive	55	Adults Mean age: 65.1 (18–90) years Male: 21 patients (38%) Female: 34 patients (62%)	NCSE 43 (78.2%) GCSE 5 (9.1%) FMSE 7 (12.7%)	Order of IV LCM 1st: 1.8% 2nd: 40% 3rd: 34.5% 4th or greater: 23.6%	50–400 mg IV (median 200 mg) Subsequent dose 50– 400 mg IV /day (median 200 mg/day)	SE cessation after administration: 70.9% (39/55) SE cessation<24 h after administration: 49.1% (27/55) Time to seizure cessation: 18 h (mean)	Overall: 8/55 (14.5%) Somnolence (5) Nausea (2) Dizziness (1) Diplopia (1) PR interval prolongation (1) AV block (1) Discontinuation: 2/55 (3.6%)
Grosso *et al.* [2014c]	Retrospective, descriptive, Italy	11	Children Mean age: 9.4 (3–16) years Male: 5 patients Female: 6 patients	Refractory SE: convulsive 6/11 (54%) non-convulsive 5/11 (46%)	LCM as fourth or later drug LCM was started after a mean latency interval of 58 h (range 22–576 h)	mean initial bolus dose of LCM: 8.6 mg/kg	SE cessation overall: 5/11 (45%)	No AEs
Poddar *et al.* [2016]	Retrospective, descriptive	9	Children mean age: 5.7 years (3 months to 16 years) Male: 4 patients Female: 5 patients	generalized: 1 complex partial: 6 (1 with secondary generalization) complex partial, myoclonic, generalized tonic 1 *epilepsia partialis continua* 1	range: 2–6	mean initial or loading dose: 8.7 mg/kg (3.3– 10 mg/kg) average total amount of IV LCM administered within the initial 24 h: 13.8 mg/kg (4.3–15 mg/kg).	efficacious in 7/9 (77.8%) patients 4/9 patients (44.4%) seizure-free	Bradycardia (1)

AE, adverse effect; AED, anti epileptic drug; AV, atrioventricular; BP, blood pressure; CI, confidence interval; CSE, convulsive status epilepticus; ECG, electrocardiogram; EEG, electroencephalogram; FMSE, focal motor status epilepticus; GCSE, generalized, convulsive status epilepticus; IV, intravenous; LCM, lacosamide; NCSE, nonconvulsive status epilepticus; OR, odds ratio; PHT, phenytoin; RSE, refractory status epilepticus; SD, standard deviation; SE, status epilepticus

cidal ideas/attempts, has been shown to be indistinguishable (LCM 4.3%, other AEDs 5.1%).

Monotherapy in focal epilepsies

The efficacy and safety of LCM monotherapy in focal epilepsy patients with partial-onset seizures have been evaluated in prospective, historical-controlled, head-to-head, and retrospective studies.

A historical-controlled, multicenter, double-blind, conversion to monotherapy study by Wechsler and colleagues enrolled 425 patients with partial-onset seizures, a mean age of 40.6 years (range 16–70 years), and 1–2 concurrent anticonvulsive drugs [Wechsler *et al.* 2014]. Patients were randomized to two subgroups and treated with a LCM dose of 400 mg/day ($n = 319$ patients) or 300 mg/day ($n = 106$ patients). Starting at 200 mg/day the LCM dose was titrated over 3 weeks. A 6-week withdrawal of background AEDs was followed by a 10-week LCM monotherapy maintenance period [Wechsler *et al.* 2014].

In patients with a LCM dose of 400 mg/day and completing the monotherapy phase ($n = 201$), seizure freedom was observed in 30 (14.9%) patients. A reduction in seizure frequency >50% compared with the baseline was observed in 122 (60.7%) patients. A total of 72 (16.9%) patients withdrew due to TEAEs. The most common reported TEAEs were dizziness (24.0%), headache (14.4%), nausea (13.4%), convulsion (11.5%), somnolence (10.4%), and fatigue (10.1%) [Wechsler *et al.* 2014].

In order to achieve monotherapy approval by the European health authorities, a prospective controlled non-inferiority trial was conducted in patients aged ⩾16 years with newly diagnosed focal epilepsy [Baulac *et al.* 2016]. LCM was compared with controlled release carbamazepine (CBZ-CR). Stepwise up-titration to the target dose (LCM: 200, 400, 600 mg/day; CBZ-CR: 400, 800, 1200 mg/day) was based on seizure control, reflecting clinical practice. Overall, 886 patients with mean ages of 41.9 (LCM) and 41.8 years (CBZ-CR) were included in the full analysis set (FAS) (LCM: 444; CBZ-CR: 442) and 805 (408; 397) in the PPS. Kaplan–Meier estimates for the proportion of patients in FAS remaining seizure-free for 6 months were 89.8% with LCM *versus* 91.1% with CBZ-CR; similar results were obtained for the PPS. Therefore, LCM was considered non-inferior to CBZ-CR [Baulac *et al.* 2016]. In the FAS, 327 (73.6%) LCM-treated and 308 (69.7%) carbamazepine-CR–treated patients completed 6 months of treatment on the last evaluated dose without having a seizure. AEs were reported by 328 (73.9%) LCM-treated and 332 (75.1%) CBZ-CR-treated patients and were the most common reason for withdrawal in 10.8% *versus* 15.6% of cases. The AEs occurring in >5% of either group were headache (13.7; 12.9%), dizziness (11.7; 8.6%), fatigue (7.2; 10.4%), nasopharyngitis (6.3; 6.6%), nausea (5.9; 5.0%), somnolence (5.4; 9.3%) and an increase in gamma glutamyl transferase (1.6; 8.1%).

There have been two uncontrolled long-term studies published. In a prospective study by Lattanzi and colleagues, 58 patients with partial-onset seizures with or without generalization and a median age of 40.5 (range, 28–47) years were converted to LCM monotherapy after 1 year of freedom from seizures on LCM add-on therapy by withdrawal of the additional AEDs [Lattanzi *et al.* 2015]. Assessments followed every 3 months up to 1 year [Lattanzi *et al.* 2015]. After 1 year, LCM monotherapy was maintained in 37 (63.8%) patients. More than half of the patients (32 patients, 55.2%) remained seizure-free during the entire follow up. Mild to moderate AEs were reported in 12 (20.8%) patients, including drowsiness ($n = 7$), dizziness ($n = 3$), and headache ($n = 2$). Fewer than three AEDs during lifelong anticonvulsive treatment appeared to be a significant predictor of seizure freedom [Lattanzi *et al.* 2015].

A retrospective study by Giraldez and colleagues examined the charts of 66 patients with a mean age of 49.4 (range, 16–92) years with partial-onset seizures with or without generalization who had been treated with LCM monotherapy [Giraldez *et al.* 2015]. The subgroups included 18 patients naïve to AEDs (Group 1) and 48 patients who had previously received another AED treatment (Group 2). Follow up comprised 0.5–54 (mean 15.5) months [Giraldez *et al.* 2015].

A total of 42 (63.6%) patients stayed seizure-free throughout follow up. After 6 and 12 months the seizure-free rates amounted to 77.6% and 72.3%. Mild-to-moderate AEs were reported in 15 patients (22.7%), the most common being somnolence/fatigue (7.5% of patients) and dizziness (6.1% of patients). Overall, 10 (15%) patients withdrew LCM therapy due to side effects (3

patients), lack of efficacy (6 patients) and other reasons (1 patient). Group differences regarding efficacy or tolerability were not significant [Giraldez *et al.* 2015].

Use in status epilepticus

Status epilepticus (SE) is a life-threatening condition and a medical emergency imposing a considerable burden on the affected person and on society in general [Kortland *et al.* 2015]. The refractory and super-refractory SEs that fail to respond to first and second line agents or even to anesthesia are associated with a high number of fatalities and high morbidity. Therefore, additional treatment options are of great interest. The efficacy and tolerability of LCM in SE have been the focus of numerous case reports and several clinical studies, most of which have employed a retrospective design. Overall, data from more than 400 patients including case studies and reports with adult SE patients and an additional pediatric SE patients are available, for details please refer to Table 5. The overall success rate for SE termination suggests a favorable role in SE treatment, with rates ranging from 81% [Hofler *et al.* 2011] to 33% [Kellinghaus *et al.* 2014] of patients. In pediatric patients, success rates in terminating SE of 45–78% are described. LCM is currently not approved for use in SE. Concurrently, most studies used LCM as an adjunctive therapy in refractory SE patients. This impacts the evaluation of LCM efficacy and may have led to an underestimation of the efficacy of LCM in SE treatment. AEDs are commonly less effective in terminating SE if used at a later position in the succession of anticonvulsive drugs [Chen and Wasterlain, 2006], which is reflected in the findings from several studies. The efficacy with later positioning decreased from 60 to 20% [Kellinghaus *et al.* 2011], 84.6–55.6% [Santamarina *et al.* 2013], and 72.2– 56.3% [Miro *et al.* 2013], respectively. A longer time from seizure onset to LCM administration also significantly reduced treatment success [Garces *et al.* 2014]. The efficacy of LCM with regard to different SE manifestations [nonconvulsive status epilepticus (NCSE), generalized convulsive status epilepticus (GCSE), focal SE] was not accounted for in most of the included studies, probably due to small sample sizes. Varying termination rates were reported among seizure types, ranging from 91% for convulsive status epilepticus (CSE) to 70% for NCSE [Hofler *et al.* 2011].

Höfler and Trinker reviewed the literature on LCM in SE published during the period from January 2009 to May 2012 [Hofler and Trinka, 2013]. A total of 10 single case reports were included, representing 10 seizures. An additional 126 seizures were extracted from nine retrospective case series. The success rate of LCM treatment was 100% in the case reports, possibly owing to publication bias. Among the two case series with 30 or more patients, success rates were 44% and 81%, respectively. The overall success rate of LCM was 56% (70/136 episodes of SE).

Since then, several additional studies on SE treatment with LCM have been published: in a prospective multicenter study using intravenous LCM as an add-on AED in refractory SE, LCM was effective in terminating SE in 64.7%. Overall, 50% of SE ended within the first 12 h after LCM application. Two mild AEs were seen, both resolving with reduced doses of LCM [Miro *et al.* 2013]. Sutter and colleagues reported results from a retrospective comparative cohort study in patients with refractory SE employing historical cohorts. No significant differences in age, SE severity or etiology were found between the groups [Sutter *et al.* 2013]. Using univariable analyses, SE duration and seizure control were altered favorably, but nonsignificantly. After adjustment for age, mortality was significantly lower in patients treated with LCM. The authors concede that the reduction in mortality was confounded by the implementation of continuous electroencephalogram (EEG) monitoring 1 year prior to the cohort change. No AEs were reported. In another retrospective study, LCM terminated seizures in 67.7% of cases. Among a total of 92 patients, 31 received LCM. When LCM was used earlier in the course of treatment (as second or third AED), the termination rate was significantly higher with LCM than without (84.6% *versus* 47.8%). No significant difference in termination rate was seen when LCM was positioned later in the AED succession. Overall, efficacy was higher when LCM was administered earlier during the course of treatment. Belcastro and colleagues reported data from 16 stroke patients with post-stroke NCSE diagnosed by video-EEG [Belcastro *et al.* 2013]. LCM was used as the first AED and ended SE in 7 of 16 cases (44%), with no significant AEs noted. The mean time from stroke onset to NCSE diagnosis was not reported. Kellinghaus and colleagues retrospectively compared the use of intravenous phenytoin to intravenous LCM in

patients with refractory SE ($n = 46$), defined as failure of the first and second anticonvulsants to stop SE [Kellinghaus *et al.* 2014]. Pretreatment using benzodiazepines and levetiracetam achieved similar results. SE ended in 40% of phenytoin patients and 33% of LCM patients. The patients in the phenytoin group had a higher rate of generalized convulsive seizures. Significant AEs were seen in 27% of the phenytoin group, and no AEs were reported in the LCM group. The authors conclude that LCM showed similar success rates to phenytoin in refractory SE with less risk of AEs. In a retrospective multicenter observational study (LACO-IV) [Garces *et al.* 2014], data from 55 patients were reviewed. LCM ended 70.9% of SE episodes, while cessation after <24 h from administration ended 49.1% of SE episodes. The treatment response was significantly better if LCM was administered earlier. AEs were reported in 8 patients (14.5%), leading to the discontinuation of LCM administration in 2 patients. Legros and colleagues compared the efficacy of 200–400 mg loading doses of LCM in SE and seizure clusters (SC) in a prospective observational study that included 25 patients [Legros *et al.* 2014]. The higher initial dose was nonsignificantly-associated with a higher degree of early SE termination and a higher response rate. Overall, 36% (9/25 patients) responded to LCM treatment. There were 4 AEs (16% of patients), all in the 200 mg group. Lang and colleagues describe an overall efficacy of 70% in patients with SE and seizure clusters upon intravenous LCM treatment. In addition to 19 patients with seizure clusters (SC), 51 patients with SE were included, but efficacy and AEs were not reported separately for these patients [Lang *et al.* 2016].

Poddar and colleagues retrospectively analyzed the efficacy and safety of LCM as an add-on treatment in nine pediatric patients (mean age 5.7 years) [Poddar *et al.* 2016]. LCM was successful in 77.8% (7/8) cases in ending SE. Overall, four patients (44%) remained seizure-free. An AE of bradycardia was observed in one child. Grosso and colleagues retrospectively analyzed data from 11 pediatric patients with a mean age of 9.4 years and SE [Grosso *et al.* 2014a]. LCM was effective in ending seizures in five patients (45%). No SAEs were reported.

Additional case reports hint at a positive effect of LCM in focal motor SE: Spalletti and colleagues describe a 39-year-old male with focal motor SE responsive to LCM as a fifth AED [Spalletti *et al.* 2013]. Hawkes and colleagues describe two additional patients with focal motor SE responsive to oral LCM as adjunctive AED [Hawkes *et al.* 2013]. A single case report suggests that LCM is effective in absence SE [Sodemann *et al.* 2014], although this is contested [d'Orsi *et al.* 2014].

The rate of AEs, including mild ones, ranged from 0–77% of patients in a review by [Hofler and Trinka, 2013]. Overall, the most common side effects are sedation, dizziness, nausea and diplopia. In studies including >15 patients treated with LCM, the rate of AEs ranged 0–77% [Kellinghaus *et al.* 2011]. Of note, Kellinghaus and colleagues suggest possible effects of other drugs given concomitantly or in rapid succession with LCM prior to the onset of AEs [Kellinghaus *et al.* 2011]. The rate of significant AEs was low in all studies. Allergic skin reactions [Kellinghaus *et al.* 2011], angioedema [Goodwin *et al.* 2011], hypotension [Kellinghaus *et al.* 2011; Cherry *et al.* 2012] as well as PR interval prolongation [Santamarina *et al.* 2013; Garces *et al.* 2014], AV block [Garces *et al.* 2014] and elevation of liver enzymes [Cherry *et al.* 2012; Legros *et al.* 2014] are described. Psychobehavioral AEs were not reported, probably due to patient characteristics. Rarely, AEs led to discontinuation of LCM therapy [Garces *et al.* 2014]. Of note, AEs are difficult to attribute to a single drug because the patients included in the study received several drugs in succession for SE treatment. No SAEs occurred in the studies in pediatric patients [Grosso *et al.* 2014c; Poddar *et al.* 2016], a smaller case series of three patients described two patients with delayed oculogyric crisis and chorea, respectively [Jain and Harvey, 2012]. LCM seems to be a safe and efficacious treatment option in SE. Data on comparative efficacy regarding other new AEDs or the choice of synergistic combinations remains elusive, only one study showed similar efficacy of LCM as compared with phenytoin or levetiracetam [Kellinghaus *et al.* 2014]. Data from the 6-Hz-induced seizure model in mice showed synergistic combinations with carbamazepine, lamotrigine, topiramate, gabapentin and levetiracetam [Shandra *et al.* 2013]. The transferability to humans is questionable. Overall, the lack of RCTs precludes further interpretation of LCM efficacy. In particular, a direct comparison of LCM with other well-tolerated intravenous drugs such as levetiracetam or valproate is missing, resulting in difficulties in clinical decision-making over which drug to use first or second.

Conclusion

In summary, LCM shows comparable efficacy with other AEDs such as zonisamide [Cox *et al.* 2014], eslicarbazepine [Rocamora, 2015], perampanel [Strzelczyk *et al.* 2015] or brivaracetam [Strzelczyk *et al.* 2016] licensed in the last decade for the treatment of partial-onset seizures. Head-to-head comparisons with other new anticonvulsants are desirable to clarify if there are any real differences in efficacy. The strength of LCM is the lack of interaction potential and the option for intravenous use in emergency situations requiring rapid up-titration. Due to its overall good tolerability, LCM use in SE is increasing. So far, the data are promising.

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