



Is Therapeutic Drug Monitoring of Lacosamide Needed in Patients with Seizures and Epilepsy?

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Published online: 16 January 2020
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Abstract

Lacosamide is an antiepileptic drug (AED) that has linear pharmacokinetics, predictable blood concentrations, and few drug interactions, setting it apart from other AEDs that require vigorous therapeutic drug monitoring (TDM) such as phenytoin and carbamazepine. However, there have been reports of altered lacosamide pharmacokinetics in some populations. The purpose of this review is to determine whether lacosamide pharmacokinetics are altered in certain patient populations, suggesting the need for TDM. A literature search of Medline, Scopus, Embase, and Cochrane trials was conducted on January 3, 2019 (and then updated on September 2, 2019) to search for articles relevant to the TDM or pharmacokinetics of lacosamide. A total of 56 relevant articles were found and included in this review. Dose of lacosamide is linearly correlated with plasma concentrations and efficacy. However, currently there is no well-established reference range. Overall, the recommended reference ranges varied from 2.2 to 20 mg/L. Lacosamide has very few clinically relevant drug–drug interactions; however, there seems to be a significant drug interaction between lacosamide and enzyme-inducer AEDs. Based on available literature, it appears that lacosamide pharmacokinetics may be altered in severe renal dysfunction, in patients on dialysis and with extremes of age. More evidence is currently needed on lacosamide pharmacokinetics in pregnancy and critical illness. While it is not practical to utilize TDM for all patients, TDM may be useful in patients taking enzyme-inducer AEDs, in patients with decreased renal function or on dialysis, and older adults.

Key Points

Dose of lacosamide is linearly correlated with plasma concentrations and efficacy. However, currently there is no well-established reference range.

Lacosamide TDM may be useful in patients taking enzyme-inducer antiepileptic drugs, in patients with decreased renal function or on dialysis, and older adults.

Further studies are needed to determine the need for lacosamide TDM during pregnancy, in pediatrics, and in critically ill patients.

1 Introduction

Lacosamide is an antiepileptic drug (AED) indicated in many countries as adjunctive therapy in adults for focal seizures [1], although indication of lacosamide is expanded in some countries for use as monotherapy and in pediatrics [2]. The mechanism of action of lacosamide is unique compared to other AEDs in that it enhances the slow inactivation of sodium channels, thereby inhibiting excessive firing of neurons [3]. Lacosamide has a more favorable side-effect profile compared to some of the older AEDs, with the most common side-effects being dizziness, headache, and nausea [4]; however, it is also known to prolong the PR interval [4, 5].

The pharmacokinetic profile of lacosamide has been well established. It has 100% oral bioavailability and reaches peak plasma concentration in 1–4 h [6]. Protein binding is minimal (< 15%) [7], and volume of distribution is about 0.6 L/kg. Elimination is 60% hepatic by CYP3A4, 2C9 and 2C19, and 40% renal [6]. The inactive metabolite formed, O-desmethyl-lacosamide, is also eliminated renally. The average half-life is predicted to be about 13 h in adults [6]. Because of its linear pharmacokinetics, predictable

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serum concentrations, and minimal drug interactions, current guidelines recommend that therapeutic drug monitoring (TDM) of lacosamide is not necessary. However, there have been reports of altered lacosamide pharmacokinetics in certain populations such as in older adults or those with impaired renal function [7]. Altered serum lacosamide disposition may result in serum concentrations that are too low to maintain efficacy, or elevated with the increased potential to cause adverse effects or toxicity, suggesting the potential need for TDM. Factors that may affect lacosamide pharmacokinetics include renal function, pregnancy status, age, and critical illness.

The aim of this review was to summarize the current evidence pertaining to lacosamide pharmacokinetics and to determine whether lacosamide pharmacokinetics are altered in certain patient populations, suggesting the need for TDM. While other reviews have discussed lacosamide TDM in a broader context [8], this review is the first to examine the potential utility of lacosamide TDM in special populations.

2 Literature Search

Medline, Scopus, Embase, and Cochrane trials databases were searched using the keywords (lacosamide OR vimpat OR copinar) AND (monitor* OR tdm OR pharmacokinetic* OR pk OR “drug administration schedul*” OR “concentration controlled”). Keywords were selected and refined with the assistance of a librarian. The search was repeated to capture any new publications. An abstract and title screening was performed independently by both authors. A full text review was performed to further refine search results. Books, reviews, animal studies, and editorials were excluded. Conference abstracts were included if they were deemed relevant and contained lacosamide blood concentrations. All primary studies that included lacosamide blood concentrations were included. Data extracted from studies included study design, population studied, number of participants, age range, proportion of male participants, lacosamide dosage range, study aim, main results and suggested reference range if included.

3 Results of Literature Search

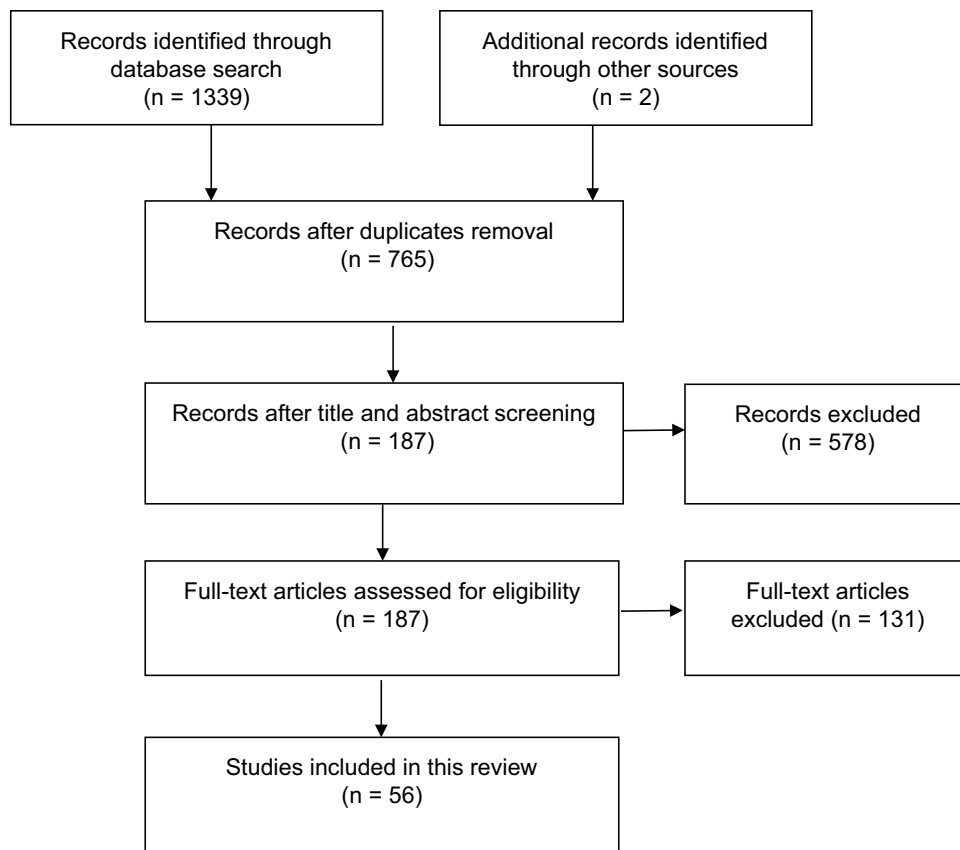
The keyword search was completed on January 3, 2019 and then updated on September 2, 2019 (Fig. 1). Medline, Scopus, Embase, and Cochrane trials produced 215, 340, 712, and 72 results, respectively, for a total of 1,339 records. Two additional records were identified through scanning the reference lists of the reviewed articles. After duplicate removal, 765 records remained. Then, 578 were excluded in the abstract screening, primarily due to irrelevance, leaving 187

for the full text review. Of those, 131 were excluded, primarily due to irrelevance, except for 2 excluded due to inability to translate to English. Therefore, a total of 56 articles were included in the discussion of this paper (12 of which were conference abstracts), including 14 randomized controlled trials (RCTs), 9 secondary analyses, 25 observational studies (10 prospective, 15 retrospective), 1 case series, and 7 case reports. Based on the GRADE working group, the quality of evidence of the included articles ranges from low to very low [9]. Table 1 depicts a summary of the included studies.

4 Therapeutic Drug Monitoring

Several AEDs such as valproic acid, carbamazepine, and phenytoin require plasma concentration monitoring as a way to ensure efficacy and avoid toxicity. Although the TDM of lacosamide is not currently routinely recommended, a number of studies have evaluated how lacosamide plasma concentration correlates with dose and clinical efficacy. Achieving a therapeutic plasma concentration is vital in seizure prevention. Almost all studies included have reported that lacosamide plasma concentrations are linearly related to the dose. Additionally, dose and plasma concentration are proportionally related to clinical efficacy [10]. For example, Ben-Menachem et al. reported increased efficacy of lacosamide in terms of percentage seizure reduction with increasing dose from 200 to 400 to 600 mg/day [11]. However, there was not a significant difference between 400 mg/day and 600 mg/day for focal seizures. In this study, when looking at secondarily generalized tonic-clonic seizures, lacosamide 600 mg/day achieved a significantly greater percentage seizure reduction than 400 mg/day (93.0% vs 59.4%, respectively). The same study also found increased adverse effects with lacosamide 600 mg/day. Similarly, a post hoc analysis looking at exposure of lacosamide and efficacy found an inverse relationship between area under the curve (AUC) and seizure probability over time [12], which is consistent with the correlation between dose and efficacy seen in other studies [10]. On the other hand, one conference abstract of a retrospective observational study looking at the efficacy of intravenous (IV) initiation of lacosamide did not find a relationship between mg/kg dose and plasma concentration [13], but this was likely due to the small sample size and the fact that investigators did not collect times of plasma samples.

Because lacosamide TDM is not routinely practiced, a well-established reference range has not been agreed upon. A few observational studies have suggested reference ranges for lacosamide plasma concentrations, with slight variation between them. Overall, the recommended reference ranges varied from 2.2 to 20 mg/L, and there does not appear to be a consensus on the most acceptable reference range. To illustrate, Payto et al. suggested a reference range of

Fig. 1 Flow diagram of literature review

2.2–19.8 mg/L after analyzing random serum samples at lacosamide doses of 200 and 400 mg/day and finding lacosamide concentrations ranging from 2.2 to 9.8 mg/L and 3.1 to 19.8 mg/L, respectively [14]. Perrenoud et al. recommended a similar but narrower reference range of 10–20 mg/L [15]. In this study they also looked at the efficacy of loading doses of lacosamide, where they found that a loading dose of at least 9 mg/kg was correlated with plasma concentrations within this reference range; however, it was not correlated with clinical response. Furthermore, Svendsen et al. recommended a range of 2.5–10 mg/L because they found that 60 out of 65 patients with good clinical efficacy of lacosamide had plasma concentrations in this range [16]. A limitation with this study was that they did not report the plasma concentrations of patients who were not experiencing efficacy from lacosamide, so we cannot be sure whether those patients also had lacosamide plasma concentrations in this range. On the other hand, one retrospective observational study attempted to define a safety range for lacosamide plasma concentrations in which adverse events do not occur [17]; however, they were unable to find a correlation. They found no significant difference in plasma concentration between those who experienced adverse effects (such as dizziness, visual disturbances, fatigue, nausea, vomiting, headache) and those who did not: 6.7 ± 4.3 mg/L versus 5.12 ± 2.2 mg/L ($p=0.27$), respectively.

While lacosamide is traditionally dosed twice daily, one study examined the concentrations of lacosamide at various times per day to describe lacosamide concentration fluctuations [18]. The mean peak drug concentration (C_{\max}) was about 10 mg/L, with a range from 4.0 to 18.3 mg/L. Thirteen patients received lacosamide twice daily, but in the four who received lacosamide three times daily, there were fewer fluctuations in serum concentrations as well as fewer adverse drug reactions. The authors concluded that dosing lacosamide three times daily may improve tolerability.

There are three studies that examined alternative methods of determining lacosamide concentrations, such as through saliva [19–21]. Saliva is a less invasive way of measuring lacosamide concentration, so it would potentially have utility in patients who require a concentration drawn but do not like needles. All three studies found a linear correlation between lacosamide concentrations in the plasma and saliva at various doses. However, in two of the studies, the mean lacosamide concentration in the saliva was consistently slightly greater than the mean lacosamide concentration in the plasma [19, 21]. The authors concluded that saliva may still be an effective way to measure lacosamide concentrations because it exhibits dose proportionality.

Two observational studies compared lacosamide plasma concentrations to cerebrospinal fluid (CSF) concentrations [22, 23]. It is relevant to determine the amount of lacosamide

Table 1 Summary of included studies

Author, year of publication	Study design	Population studied (seizure types)	N	Age, years Range (average \pm SD)	Sex male <i>n</i> (%)	Lacosamide dosage range	Study aim and main results	Suggested reference range
<i>Therapeutic drug monitoring</i>								
Ben-Menachem et al., 2007 [11]	Multicenter, double-blind, placebo-controlled randomized trial	Adults (focal)	418 (safety) 415 (efficacy)	18–68 (39.9 \pm 11.25)	46	200–600 mg/day (administered PO BID)	<p>AIM: To evaluate efficacy and safety of increasing doses of adjunctive lacosamide and assess for pharmacokinetic interactions with concomitant AEDs</p> <p>RESULTS: Median % reduction in seizure frequency was 10%, 26%, 39% and 40% for placebo, lacosamide 200 mg/day, 400 mg/day and 600 mg/day, respectively (400 and 600 mg/day were significantly different from placebo)</p> <p>AEs that appeared dose-related were dizziness, nausea, fatigue, ataxia, vision abnormalities, diplopia, vertigo, nystagmus (more common in 600 mg/day group)</p> <p>Lacosamide plasma concentrations at steady state were dose proportional. For 200 mg/day, 400 mg/day and 600 mg/day, mean \pm SD plasma concentrations were 4.99 \pm 2.51, 9.35 \pm 4.22, and 12.46 \pm 5.80 mg/L, respectively.</p>	NR
Brandt et al., 2018 [19]	Open-label, single-center prospective observational study	Adult inpatients who were prescribed lacosamide	24	20–64	NR	50–650 mg/day (mean 381 mg)	<p>AIM: To explore the correlation between steady-state lacosamide concentrations in the plasma and saliva at various doses</p> <p>RESULTS: Mean lacosamide concentration in serum: 7.45 \pm 3.45 mg/L (fasting: 6.30 \pm 3.11) and mean lacosamide concentration in saliva: 8.20 \pm 4.61 mg/L (fasting: 6.73 \pm 3.96). Difference between concentrations was not significant but there was a slightly higher concentration in saliva</p> <p>Concentrations of lacosamide in saliva and serum were proportional ('strong linear correlation') ($r=0.860$ for fasting, $r=0.874$ for all)</p> <p>Better correlation between lacosamide concentration in serum and saliva and lacosamide dose/kg ($r=0.690$ for serum; 0.578 for saliva, $P<0.01$) when patients receiving enzyme-inducing AEDs were excluded from analysis ($r=0.749$ for serum, 0.671 for saliva, $P<0.01$)</p> <p>Authors conclude that the high correlation between saliva and serum lacosamide doses may permit the utility of saliva for TDM of lacosamide</p>	NR

Table 1 (continued)

Author, year of publication	Study design	Population studied (seizure types)	N	Age, years Range (average \pm SD)	Sex male <i>n</i> (%)	Lacosamide dosage range	Study aim and main results	Suggested reference range
Schaefer et al., 2015 [40]	Conference abstract; pharmacokinetic simulation and comparison to phase I and a phase IIIb study	N/A	NR	NR	NR	200 mg PO/IV loading dose	<p>AIM: To determine whether a loading dose of lacosamide will achieve similar plasma concentrations to lacosamide at steady state through simulations</p> <p>RESULTS: PO/IV lacosamide loading dose achieved faster therapeutic plasma concentrations compared with the traditional titration method of lacosamide</p> <p>These simulations resulted in similar plasma concentrations to those seen in clinical trials in adults with focal seizures on lacosamide 200 mg/day</p>	NR
Chung et al., 2010 [27]	Randomized controlled trial	Patients (focal)	405	(38.3 \pm 12.13)	49.4	400 and 600 mg/day given BID	<p>AIM: To evaluate efficacy of adjunctive lacosamide for focal seizures</p> <p>RESULTS: Median percent reduction in seizure frequency per 28 days for placebo, lacosamide 400, and lacosamide 600 was 20.8%, 37.3%, and 37.8%, respectively (significant from placebo)</p> <p>Efficacy for secondarily generalized tonic-clonic seizures was dose proportional, with greater percent reduction with lacosamide 600 vs 400 (93.0% vs 59.4%)</p> <p>Dose-related TEAEs reported with an incidence of at least 10% were dizziness, nausea, diplopia, blurred vision, vomiting, tremor</p> <p>Mean lacosamide plasma concentration was dose proportional; at the end of the titration period, it was 7.75 and 9.89 mg/L for lacosamide 400 and 600, and during maintenance period was 7.19 and 9.50 mg/L</p> <p>Generally, there was no effect on plasma concentrations of other AEDs</p>	NR

Table 1 (continued)

Author, year of publication	Study design	Population studied (seizure types)	N	Age, years Range (average \pm SD)	Sex male <i>n</i> (%)	Lacosamide dosage range	Study aim and main results	Suggested reference range
Chung et al., 2010 [10]	Pooled analysis of three RCTs (phase II/III trials)	Patients (focal)	1,294	Average: 38.6	49	200, 400 or 600 mg/day	<p>AIM: To evaluate a large pool of patients on lacosamide for efficacy, safety, and pharmacokinetics</p> <p>RESULTS: All lacosamide doses were significantly efficacious in reducing median percent seizures and improving 50% responder rate compared with placebo Lacosamide 600 mg/day group experienced more TEAEs, but there was no dose proportionality observed for serious TEAEs Using an E_{max} model, there was high interpatient variability. E_{max}: $71\% \pm 30\%$, (range: 0.06–100%); AUC50: 35.9 ± 185.6 mg/L·h (range: 0–3,998) Authors conclude that the E_{max} model demonstrates that the current dosing range for lacosamide (200–600 mg/day) is acceptable, but since an established therapeutic range is not available, they do not recommend routinely monitoring serum concentrations</p>	NR
Greenaway et al., 2011 [20]	Prospective observational	Patients with intractable epilepsy	98	19–76 (43 \pm 12)	52	50–550 mg PO (mean \pm SD: 242 \pm 99 mg), divided BID Daily dose in body weight: 0.4–8.5 mg/kg (3.3 \pm 1.6 mg/kg)	<p>AIM: To investigate the correlation between lacosamide dose, serum concentration, and saliva concentration</p> <p>RESULTS: Lacosamide dose was linearly related to total and free lacosamide serum concentrations ($r^2 = 0.825, 0.815$, respectively) Mean lacosamide serum total concentration was 22 ± 12 μmol/L and serum-free concentration was 2.1 ± 1.2 μmol/L; they were linearly related. Thus, protein binding was calculated to be $91 \pm 4\%$ (in contrast to published value of <30%) Lacosamide serum total concentration and saliva concentration were linearly related ($r^2 = 0.842$), as was lacosamide serum-free concentration and saliva ($r^2 = 0.828$)</p>	40–80 μ mol/L (10–20 mg/L)

Table 1 (continued)

Author, year of publication	Study design	Population studied (seizure types)	N	Age, years Range (average \pm SD)	Sex male <i>n</i> (%)	Lacosamide dosage range	Study aim and main results	Suggested reference range
Hillenbrand et al., 2011 [17]	Retrospective observational	Patients with uncontrolled epilepsy	70	17–68 Median: 37.4	47	NR	<p>AIM: To identify a range of lacosamide plasma concentrations in which typical adverse events do not occur</p> <p>RESULTS: 46% of patients experienced AEs. There was no significant difference in mean mg/kg dose of lacosamide when comparing patients who experienced AEs to those who did not. For example, the mean serum concentration of patients who experienced dizziness was 6.7 ± 4.3 mg/L versus patients without AEs was 5.12 ± 2.2 mg/L ($p=0.27$)</p> <p>Upon further analysis, authors found that patients on concomitant sodium channel blocker AEDs experienced significantly greater incidence of dizziness ($p=0.03$).</p> <p>Because authors did not find correlation between mg/kg dose and AEs, no safety range could be defined</p>	NR
Lindauer et al., 2017 [12]	Post hoc analysis of SP0993 (multicenter, double blind RCT comparing lacosamide and carbamazepine)	Patients with newly diagnosed epilepsy (focal or generalized tonic-clonic)	883	16–87 (42.0 ± 42.6)	54.9	200, 400, or 600 mg/day	<p>AIM: To model and describe the effect of increasing dose of lacosamide as monotherapy on time-to-seizure</p> <p>RESULTS: Authors identified an inverse relationship between AUC and seizure probability/hazard ratio</p> <p>Baseline seizure severity was predictive of seizure probability in the trial and benefited more from lacosamide 400 mg/day than 200 mg/day</p>	NR
May et al., 2015 [22]	Retrospective observational	Patients with epilepsy	21 total; 19 with time-matched CSF and serum samples	18–65 (46.0 ± 14.6)	28.6	50–600 mg/day Mean \pm SD: 331 \pm 153 mg	<p>AIM: To compare CSF and serum concentrations of lacosamide at steady state</p> <p>RESULTS: Mean serum lacosamide concentration: 8.16 ± 3.82 mg/L (range 2.29–15.45), which was found to be dose proportional</p> <p>Mean CSF lacosamide concentration: 7.37 ± 3.73 mg/L (range 1.24–14.95), which was also found to be dose proportional</p> <p>Linear relationship between CSF concentration and serum concentration, but lacosamide concentration in CSF was about 15% lower than in serum</p> <p>No correlation found between CSF-to-serum concentration ratio and lacosamide dose</p>	NR

Table 1 (continued)

Author, year of publication	Study design	Population studied (seizure types)	N	Age, years Range (average \pm SD)	Sex male <i>n</i> (%)	Lacosamide dosage range	Study aim and main results	Suggested reference range
Michelhaugh et al., 2015 [23]	Prospective observational	Adults undergoing craniotomy. Group 1: lacosamide as ongoing treatment (min 2 weeks) Group 2: lacosamide-naive	30	19–81 (group 1: 45; group 2: 46)	50	200 mg IV over 15 min single dose (CSF and serum sample varied between 16 and 140 min after end of infusion) mean \pm SD: Group 1: 2.31 \pm 0.69 mg/kg Group 2: 2.80 \pm 0.60 mg/kg	AIM: To compare lacosamide serum concentration in blood with that in CSF in both lacosamide-naive patients and patients treated with lacosamide for a minimum of 2 weeks RESULTS: Serum concentration of group 1: 9.53 \pm 3.3 mg/L; group 2: 5.75 \pm 1.7 mg/L (significant difference). Note: group 2 received significantly higher mg/kg dose CSF concentration of group 1: 7.1 \pm 3.5 mg/L; group 2: 3.1 \pm 1.5 mg/L. (significant difference) Found positive correlation between lacosamide concentration in serum and CSF in group 1 but not in group 2 No correlation between time interval between dose and sampling and CSF concentration in both groups, but there was a significant correlation between time interval and CSF/serum lacosamide ratio in group 2 No difference between CSF concentrations in those with and without concomitant AEDs Authors conclude this demonstrates that serum concentration is an appropriate surrogate for CSF concentrations of lacosamide at steady state in both chronically treated and lacosamide-naive patients	NR
Morris et al., 2015 [13]	Conference abstract (retrospective observational)	Inpatients (not specified)	45	NR	NR	200 mg IV	AIM: To assess the efficacy of IV initiation of lacosamide in patients with epilepsy in an inpatient setting RESULTS: Blood concentrations (<i>n</i> = 16) after first 200 mg IV dose (did not specify time of collection) ranged from 0–12.1. (4 concentrations of 0 were actually obtained prior to first dose of lacosamide). Average of remaining 12 concentrations was 7.09 mg/L Authors did not observe a relationship between mg/kg dose and blood concentration	NR
Payto et al., 2014 [14]	Conference abstract (prospective observational)	Adults (focal)	23 (45 serum samples)	NR	30.4	200–400 mg/day PO	AIM: To establish an expected therapeutic range of serum concentrations for lacosamide and its metabolite from random serum samples RESULTS: Patients on lacosamide 200 mg/d had range of serum concentrations between 2.2 and 9.8 mg/L and those on 400 mg/d had range of serum concentrations between 3.1 and 19.8 mg/L	2.2–19.8 mg/L

Table 1 (continued)

Author, year of publication	Study design	Population studied (seizure types)	N	Age, years Range (average \pm SD)	Sex male <i>n</i> (%)	Lacosamide dosage range	Study aim and main results	Suggested reference range
Perrenoud et al., 2017 [15]	Retrospective observational	Adult patients (SE)	40	34–88 Median: 67 Responders: 67 Non-responders: 69	48	100–800 mg IV loading dose Median: 600 mg	AIM: To investigate the relationship between lacosamide IV loading dose, serum concentrations, and clinical response RESULTS: Mean lacosamide serum concentration was 10.0 mg/L (range: 2.4–24.8 mg/L), sampled at median time 15.9 h after loading dose (range: 6.25–34.75 h). Loading dose of ≥ 9 mg/kg resulted in concentrations within reference range, but was not correlated with clinical response Lacosamide was effective in 40% of cases, but there was no correlation found between loading dose and response	10–20 mg/L
Sattler et al., 2011 [18]	Retrospective observational	Patients	17 (21 serum concentrations)	22–55		200–600 mg/day PO (administered BID or TID)	AIM: To gain understanding of lacosamide serum concentrations throughout the day RESULTS: Peak concentration occurred between 1 and 3 h after administration of lacosamide Mean C_{max} was 9.7 ± 4.6 mg/L (range: 4.0–18.3) Lacosamide was given TID in 4 patients, which showed decreased serum concentration fluctuations in all, and decreased AEs	NR
Svensden et al., 2017 [16]	Retrospective observational	Patients in Norway with refractory epilepsy (unspecified seizure type)	344	4–86 (median: 39) 82% adults	48	50–1,500 mg/day PO	AIM: To assess the pharmacokinetics of lacosamide in relation to efficacy and tolerability RESULTS: Linear correlation between dose and serum concentration No sex differences in doses and serum concentrations found C/D ratio was increased in elderly by 28% compared with adults (= significant decreased clearance). No difference between younger patients and adults Concomitant use of enzyme-inducing AEDs = 23% Decrease in C/D ratio compared with neutral/monotherapy (= significant increased clearance). Concomitant valproate or oxcarbazepine/eslicarbazepine did not alter C/D ratios Lacosamide serum concentrations at steady state: 3.3–69 μ mol/L 60/65 patients experiencing efficacy from lacosamide had serum concentration within range of 10–40 μ mol/L	10–40 μ mol/L (2.5–10 mg/L)

Table 1 (continued)

Author, year of publication	Study design	Population studied (seizure types)	N	Age, years Range (average \pm SD)	Sex male <i>n</i> (%)	Lacosamide dosage range	Study aim and main results	Suggested reference range
<i>Drug-drug/drug-formulation interactions</i>								
Biton et al., 2008 [36]	Randomized, double-blind, double-dummy trial	Inpatients currently on lacosamide (focal)	60	19–61 (41.7 \pm 9.80)	42	200–600 mg/day IV/PO IV administered over 30 or 60 min	AIM: To assess the safety, tolerability, and pharmacokinetics of lacosamide administered IV versus PO RESULTS: In both PO and IV lacosamide, a small increase in PR interval was observed Generally, seizure pattern and frequency remained consistent with control prior to starting the trial 60 min infusion (of lacosamide or placebo): C_{max} of PO lacosamide was 4.69 \pm 1.78 μ g/ml·kg/mg and AUC was 40.18 \pm 15.90 μ g·h/ml·kg/mg, and IV lacosamide C_{max} was 5.01 \pm 1.25 μ g/ml·kg/mg and AUC was 38.60 \pm 11.23 μ g·h/ml·kg/mg 30 min infusion (of lacosamide or placebo): C_{max} of PO lacosamide was 4.03 \pm 1.73 μ g/ml·kg/mg and AUC was 36.91 \pm 18.59 μ g·h/ml·kg/mg, and IV lacosamide C_{max} was 4.56 \pm 1.16 μ g/ml·kg/mg and AUC was 33.55 \pm 10.95 μ g·h/ml·kg/mg C_{max} of IV lacosamide was similar but slightly increased to that of PO	NR
Cawello et al., 2010 [25]	Randomized, open-label, multiple-dose trial	Healthy white male volunteers	37	Trial A: 33.2 \pm 6.2 Trial B: 33.1 \pm 6.0	100	200 mg BID	AIM: To investigate the pharmacokinetic interaction between lacosamide and carbamazepine RESULTS: Lacosamide C_{trough} reached steady state after 3 days and was not significantly affected by coadministration with carbamazepine, nor was AUC and $C_{max(ss)}$. Mean $C_{max(ss)}$ of lacosamide alone was 9.1 \pm 1.6 mg/L vs with carbamazepine was 9.9 \pm 2.0. Authors conclude that lacosamide and carbamazepine have no relevant clinical effect on each others pharmacokinetics	NR
Cawello et al., 2012 [24]	Open-label, randomized, multiple dose pharmacokinetic trials	Healthy volunteers	31	22–44 Group A1: 22–36 (29.5 \pm 5.4) Group A2: 23–43 (33.0 \pm 6.1) Group B1: 23–44 (29.0 \pm 6.7) Group B2: 21–43 (30.9 \pm 6.2)	100	100 mg PO BID then titrated to 200 mg BID on 3 rd day	AIM: To determine effect of lacosamide on steady-state pharmacokinetics of valproic acid, and effect of valproic acid on steady-state pharmacokinetics of lacosamide RESULTS: Lacosamide had no effect on mean steady-state valproic acid plasma concentrations and vice versa Authors conclude that using valproic acid and lacosamide concomitantly does not necessitate dose adjustment in either medication	NR

Table 1 (continued)

Author, year of publication	Study design	Population studied (seizure types)	N	Age, years Range (average \pm SD)	Sex male <i>n</i> (%)	Lacosamide dosage range	Study aim and main results	Suggested reference range
Cawello et al., 2012 [37]	Two randomized, open-label, single-dose studies: A: 2-way B: 3-way	Healthy Caucasian volunteers	A: Safety set (SS): 24 pharmacokinetics set (pharmacokinetics S): 16 B: 27	A: 20–45 (31.3 \pm 8.8) Pharmacokinetics S: 21–45 (32.6 \pm 8.7) B: 18–45 (32.4 \pm 6.9)	100	200 mg PO/IV (IV infused over 15 min in study A and 30 or 60 min in study B) single dose	AIM: To determine the bioequivalence of lacosamide PO and IV RESULTS: In study A, t_{max} of IV (infused over 15 min) was 15 min while t_{max} of PO was 1.5 h. In study B, t_{max} of IV over 30 min was 0.5 h, IV over 60 min was 1 h, PO was 1.25 h AUC for PO and IV were very similar, demonstrating that PO lacosamide has 100% bioavailability Study A: mean C_{max} of 15-min infusion and PO tab was 5.72 (90% CI 36.3) mg/L and 4.76 90% CI 23.6) mg/L, respectively Study B: mean C_{max} of 30-min infusion, 60-min infusion, and PO tablet was 5.76, 5.26, and 4.93 mg/L, respectively 30- and 60-min infusions of 200 mg lacosamide were found to be bioequivalent to oral lacosamide	NR
Cawello et al., 2012 [6]	Open-label single-dose randomized trial	Healthy volunteers	10	30–55 (40.5 \pm 9.0)	100	100 mg IV or PO (liquid)	AIM: To compare the pharmacokinetics of C-14-labeled lacosamide in healthy volunteers between a single oral dose and a single IV dose RESULTS: Total reactivity C_{max} in plasma after PO dose was 3.362 \pm 0.603 and after IV was 3.384 \pm 0.327 μ g equiv/mL Mean plasma concentrations were almost equivalent between IV and PO, indicating the high bioavailability of lacosamide	NR

Table 1 (continued)

Author, year of publication	Study design	Population studied (seizure types)	N	Age, years Range (average \pm SD)	Sex male <i>n</i> (%)	Lacosamide dosage range	Study aim and main results	Suggested reference range
Cawello et al., 2013 [21]	Randomized, open-label, crossover phase I trial	Healthy Caucasian volunteers	16	21–40 (28.8 \pm 5.7)	100	200 mg PO (tablets or 20 mL of 10 mg/mL syrup)	<p>AIM: To compare bioequivalence and pharmacokinetic parameters between lacosamide tablet and syrup formulations in both plasma and saliva</p> <p>RESULTS: For tablet and syrup, mean lacosamide plasma t_{max} was 1 and 0.5 h, mean plasma C_{max} was 5.26 and 5.14 mg/L, and AUC was 84.51 and 83.31 mg·h/L, demonstrating bioequivalence</p> <p>Mean lacosamide concentration in saliva after tablet was consistently greater than mean concentration in plasma by 3–10%.</p> <p>Using saliva and plasma lacosamide concentrations, authors determined plasma protein binding of lacosamide to be < 15% because of high ratio of saliva to total plasma concentrations</p> <p>Authors conclude that saliva may be utilized to determine lacosamide concentrations immediately after tablet ingestion or 1–2 h after syrup ingestion (to prevent concentration reflecting residual syrup in mouth)</p>	NR
Cawello et al., 2013 [33]	Pharmacokinetic study: open-label, one-arm trial	Healthy premenopausal, non-pregnant female volunteers	37	(30.5 \pm 5.3)	0	200 mg BID for days 3–11 (of cycle), then single 200 mg dose on morning of day 12	<p>AIM: To evaluate the effect of lacosamide on ovulation suppression, and whether a pharmacokinetic interaction between lacosamide and oral contraceptives exists</p> <p>RESULTS: Ovulation suppression (confirmed by serum progesterone concentrations) was achieved both in OC alone and OC + lacosamide, so lacosamide did not alter efficacy of OC</p> <p>Pharmacokinetic parameters of ethinyl estradiol and levonorgestrel for OC vs OC + lacosamide were all within 90% CI for bioequivalence, except $C_{max(ss)}$ of EE which was higher in OC + lacosamide (upper limit of CI slightly above 125%)</p> <p>OC did not seem to have an effect on pharmacokinetics of lacosamide. Mean lacosamide $C_{max(ss)}$ was 13.8 \pm 2.2 mg/L, t_{max} was 1.1 \pm 0.4 h, and AUC_(ss) was 113.5 \pm 20.7 mg·h/L</p>	NR

Table 1 (continued)

Author, year of publication	Study design	Population studied (seizure types)	N	Age, years Range (average \pm SD)	Sex male <i>n</i> (%)	Lacosamide dosage range	Study aim and main results	Suggested reference range
Cawello et al., 2014 [34]	Pharmacokinetic study: Phase I, randomized, crossover trial	Healthy volunteers	36	(36.0 \pm 6.9)	100	Treatment A: 200–600 mg/day, given BID Treatment B: lacosamide 300 mg/day on day 1 and 8	AIM: To investigate pharmacokinetic effects between lacosamide and omeprazole, a known substrate of CYP2C19 RESULTS: Treatment A: Pharmacokinetic parameters of omeprazole were highly variable, on average about 10% higher with lacosamide coadministration, but still within range for bioequivalence Mean lacosamide C_{trough} at steady state at day 7 and 8 was 7.3 mg/L Treatment B: Pharmacokinetic parameters of lacosamide were similar with and without omeprazole coadministration, and all were in range for bioequivalence	NR
Cawello et al., 2014 [35]	Phase I, multiple dose, randomized, double-blind, placebo-controlled crossover trial	Healthy white males	20	(36.8 \pm 5.4)	100	200 mg PO BID	AIM: To examine the effect of concomitant lacosamide and digoxin on pharmacokinetics of each medication RESULTS: Pharmacokinetics of digoxin did not significantly change with coadministration of placebo vs lacosamide and point estimates (90% CIs) of $AUC_{(ss)}$ and $C_{\text{max}(ss)}$ remained in the acceptable range for bioequivalence (0.8–1.25) The $AUC_{(ss)}$ and $C_{\text{max}(ss)}$ at $t_{\text{max}(ss)}$ of lacosamide with digoxin were compared to trials with lacosamide alone and did not differ significantly. Mean $AUC_{(ss)}$ was 83.2 \pm 11.4 mg·h/L with digoxin, compared with 82.7 \pm 13.9 and 79.7 \pm 13.4 alone. Mean $C_{\text{max}(ss)}$ was 9.5 \pm 1.1 mg/L with digoxin compared with 9.5 \pm 1.3 and 9.1 \pm 1.6 alone. $T_{\text{max}(ss)}$ was 0.93 \pm 0.61 h with digoxin compared with 0.73 \pm 0.26 and 2.4 \pm 1.0 alone	NR
Cawello, 2015 [26]	Conference abstract: Post hoc analysis of RCT	Patients (focal)	NR	16–70	NR	300 or 400 mg/day PO	AIM: To analyze lacosamide blood concentrations in patients undergoing conversion from using lacosamide as adjunct therapy to monotherapy RESULTS: Author analyzed geometric mean ratios of monotherapy and adjunctive therapy for dose-normalized pharmacokinetic parameters of lacosamide Ratios were similar between monotherapy and adjunctive therapy for $C_{\text{max}(ss)}$, $C_{\text{trough}(ss)}$, $AUC_{\text{tau}(ss)}$, ranging from 1.039 to 1.071. Mean concentration was also very similar	NR

Table 1 (continued)

Author, year of publication	Study design	Population studied (seizure types)	N	Age, years Range (average \pm SD)	Sex male <i>n</i> (%)	Lacosamide dosage range	Study aim and main results	Suggested reference range
Contin et al., 2013 [29]	Prospective observational	Patients with epilepsy (unspecified seizure type)	75	Group A: (36 \pm 16) Group B: (35 \pm 18)	55	Mean \pm SD Group A: 283 \pm 110 Group B: 286 \pm 101	<p>AIM: To determine the impact of concomitant AEDs on lacosamide steady-state plasma concentrations</p> <p>RESULTS: Median values of lacosamide plasma conc-to-weight-adjusted dose ratio (L/D) were significantly decreased by about 30% with concomitant strong enzyme inducers: 0.94 (0.75–1.27) vs 1.35 (1.16–1.74)</p> <p>Plasma concentration of lacosamide was proportional to dose per body weight; however, there was much variability between patients</p> <p>No significant differences in LD of lacosamide between sexes</p>	NR
Fountain et al., 2013 [38]	Phase 3b, multicenter open-label trial	Patients (focal)	100	(39.0 \pm 11.66)	51	IV loading dose (200, 300, 400 mg) over 15 min followed 12 h later by equivalent daily PO dose given BID x6.5 days	<p>AIM: To assess safety and tolerability of a single IV loading dose of lacosamide over 15 min then PO lacosamide maintenance therapy in lacosamide-naive patients on 1–2 concomitant AEDs</p> <p>RESULTS: Mean C_{max} plasma (\pm SD) measured immediately after IV lacosamide dose was dose proportional. 200 mg: 6.596 \pm 2.218 mg/L; 300 mg: 9.319 \pm 3.765 mg/L; 400 mg: 12.330 \pm 4.118 mg/L</p> <p>C_{trough} measured 12 h post-infusion and prior to PO dose. Mean: 200 mg: 2.927 \pm 1.276 mg/L; 300 mg: 3.243 \pm 1.162 mg/L; 400 mg: 4.500 \pm 1.625 mg/L</p> <p>Day 2 troughs: 3.379 \pm 1.694, 3.844 \pm 1.730, 4.917 \pm 1.499 mg/L</p> <p>Authors conclude that a single IV loading dose of lacosamide over 15 min provides similar plasma concentrations as equivalent daily oral doses at steady state</p>	NR

Table 1 (continued)

Author, year of publication	Study design	Population studied (seizure types)	N	Age, years Range (average \pm SD)	Sex male <i>n</i> (%)	Lacosamide dosage range	Study aim and main results	Suggested reference range
Krauss et al., 2010 [39]	Prospective observational	Adult patients (focal)	160	(39.4 \pm 11.2)	51	200–800 mg/day IV, infused over 10, 15, and 30 min, given BID	<p>AIM: To assess safety and tolerability of various durations of IV lacosamide infusions (for 2–5 days) in patients on maintenance lacosamide treatment</p> <p>RESULTS: There was no relationship between AEs and infusion duration</p> <p>Headache and dizziness appeared dose related</p> <p>Seizure control remained stable while on IV lacosamide</p> <p>Lacosamide plasma concentrations were dose proportional and similar for all infusion durations. C_{max} and C_{trough}, respectively, were 5.5 ± 1.2 and 2.6 ± 0.8 mg/L for 200 mg/day, 10.5 ± 2.5 and 4.7 ± 1.4 for 400 mg/day, 15.9 ± 4.1 and 7.7 ± 2.7 for 600 mg/day, and 23.0 ± 6.4 and 11.0 ± 3.5 for 800 mg/day</p>	NR
Halasz et al., 2009 [4]	Randomized double-blind placebo-controlled trial	Patients with uncontrolled seizures (focal)	ITT: 477 Per protocol: 399	16–70 (37.8 \pm 11.88)	51.5	200–400 mg/day (100 mg BID or 200 mg BID)	<p>AIM: To assess safety and efficacy of lacosamide with concomitant AEDs</p> <p>RESULTS: Median % reduction in seizure frequency/28 days: 200 mg/day: 35.3%, 400 mg/day: 36.4% (compared to placebo at 20.5%, both statistically significant)</p> <p>Lacosamide plasma concentrations were dose proportional. Mean plasma concentration 200 mg/day: 3.8 mg/L ; 400 mg/day: 7.4 mg/L</p> <p>Mean plasma concentrations did not seem to be affected by concomitant AEDs (exception: decrease in oxcarbazepine monohydroxy metabolite concentration in lacosamide 400 mg/day group 4.2 ± 7.53 mg/L)</p>	NR

Table 1 (continued)

Author, year of publication	Study design	Population studied (seizure types)	N	Age, years Range (average \pm SD)	Sex male n (%)	Lacosamide dosage range	Study aim and main results	Suggested reference range
May et al., 2018 [28]	Retrospective observational	Patients with epilepsy (unspecified seizure type)	973	1.6–80.4 (34.5 \pm 15.9) Median 33.7	51.4	25–1,050 mg/day PO Mean: 326 \pm 126 Median: 300	<p>AIM: To describe the influence of concomitant AEDs (enzyme-inducing: carbamazepine, phenytoin, phenobarbital, primidone, and enzyme-inhibiting: valproic acid) on lacosamide trough serum concentrations</p> <p>RESULTS: Lacosamide trough concentrations were significantly lower (-21%) in children 6–12 yrs than adults 18–60 yrs, and concentrations were slightly higher ($+20\%$) in older patients >60 yrs. When lacosamide was dose adjusted for V_d, they found significant effects of age on serum concentrations and coadministration of AEDs</p> <p>Sex had no significant effect on lacosamide concentrations; however, when adjusted for V_d, lacosamide concentrations in females were significantly lower (12%) compared with males</p> <p>Enzyme-inducing AEDs significantly decreased lacosamide concentrations (-30% with carbamazepine to -40% with methsuximide). This was more marked in children (-46%) than adults.</p> <p>Enzyme-inhibiting AEDs did not significantly affect lacosamide trough concentrations</p>	NR
Novy et al., 2011 [32]	Case series	Patients (simple and complex focal, and generalized tonic-clonic)	7	22–77	14.3	200 mg/day	<p>AIM: To describe cases of patients on lacosamide with other sodium-channel blocking AEDs and investigate a potential pharmacodynamic interaction among them</p> <p>RESULTS: All 7 patients had lacosamide serum concentrations within or below a suggested reference range (1.3–12 mg/L)</p> <p>Authors conclude that these CNS AEs were likely due to a pharmacodynamic interaction with other sodium-channel blocking AEDs</p>	NR

Table 1 (continued)

Author, year of publication	Study design	Population studied (seizure types)	N	Age, years Range (average \pm SD)	Sex male <i>n</i> (%)	Lacosamide dosage range	Study aim and main results	Suggested reference range
Ota et al., 2018 [31]	Conference abstract (prospective observational)	Japanese patients with epilepsy	49	(43 \pm 17)	49	Mean \pm SD: 168 \pm 118 mg/day	<p>AIM: To investigate the pharmacokinetics of lacosamide when coadministered with other inducer AEDs</p> <p>RESULTS:</p> <p>Mean serum concentration of lacosamide was 5.4 \pm 3.5 mg/L and was dose proportional</p> <p>45% of patients showed > 75% seizure reduction at dose 209 \pm 124 mg/day and serum concentration 5.0 \pm 3.2 mg/L</p> <p>The slope of regression line (a) of dose-concentration relationship varied depending on type of concomitant AED:</p> <p>inducer (-)/inhibitor (-): a = 0.0296, r = 0.95317</p> <p>inducer (+)/inhibitor (-): a = 0.0071, r = 0.11157</p> <p>inducer (-)/inhibitor (+): a = 0.0214, r = 0.54157</p> <p>inducer (+)/inhibitor (+): a = 0.0325, r = 0.8225</p> <p>Authors conclude that coadministration of AED may have an effect on lacosamide dose-concentration relationship, depending on the type of AED</p>	NR
Remi and Zwanzig, 2016 [41]	Case report	Patient with epilepsy	1	41	M	200 mg SC BID x2 doses	<p>AIM: To describe the use and serum concentrations of SC lacosamide in a palliative patient with epilepsy</p> <p>RESULTS:</p> <p>Patient previously on lacosamide 400 mg/day PO as part of antiepileptic regimen, but lost ability to swallow medications and family favored SC medications to IV</p> <p>Off-label SC lacosamide was given to patient at dose of 200 mg undiluted IV solution over 10 min SC x2 doses</p> <p>Immediately before SC injection, lacosamide serum concentration was 3.56 mg/L, peak lacosamide concentration (50 min after SC dose) was 5.44 mg/L, and trough concentration was 3.67 mg/L</p> <p>Patient did not experience any seizures on this regimen</p>	1–10 mg/L

Table 1 (continued)

Author, year of publication	Study design	Population studied (seizure types)	N	Age, years Range (average \pm SD)	Sex male <i>n</i> (%)	Lacosamide dosage range	Study aim and main results	Suggested reference range
<i>Pregnancy</i>								
Ylikotila et al., 2015 [43]	Case report	Pregnant woman (focal secondarily generalized, status epilepticus)	1	36	F	300 mg/day for 5 days then 100 mg BID	<p>AIM: To describe the lacosamide concentrations in breast milk and cord blood</p> <p>RESULTS: Woman was treated with lacosamide starting at week 8 of pregnancy and on, with planned caesarean section at week 36</p> <p>Boy was born with no malformations but was small for gestational age</p> <p>Lacosamide concentrations from mother and cord blood immediately after delivery were 3.8 ± 1.1 mg/L and 3.9 ± 1.2 mg/L, respectively, demonstrating that lacosamide must freely cross the placenta.</p> <p>Lacosamide concentration in breast milk (5 days postpartum) was 0.4 ± 0.2 mg/L</p> <p>Blood concentration in child (8 days postpartum) was 0.2 ± 0.1 mg/L. Note: approximately half of ingested milk was from mother</p> <p>Estimated RID of lacosamide is 1.8%</p> <p>Follow-up until child was 7 months old: showed normal development</p>	NR

Table 1 (continued)

Author, year of publication	Study design	Population studied (seizure types)	N	Age, years Range (average \pm SD)	Sex male <i>n</i> (%)	Lacosamide dosage range	Study aim and main results	Suggested reference range
<i>Renal impairment</i>								
Cawello et al., 2013 [7]	Open-label, single dose, Phase I trial (prospective observational)	Caucasian adults (healthy volunteers, mild, moderate, severe renal impairment, ESRD)	40 (8 in each group)	18–70 Group 1 (CrCl \geq 80 mL/min): 44–66 (56.4 \pm 8.2) Group 2 (CrCl 50–80 mL/min): 25–63 (50.9 \pm 12.8) Group 3 (CrCl 30–50 mL/min): 37–65 (47.6 \pm 10.2) Group 4 (CrCl 20–30 or < 20 mL/min): 38–68 (57.9 \pm 10.7) Group 5 (ESRD; CrCl < 15 mL/min): 27–54 (43.1 \pm 8.8)	63	100 mg single dose PO ESRD: 2 single PO doses in fixed order with \geq 6 day washout period. Treatment A: 100 mg on HD-free day. Treatment B: 100 mg 2.5 h before start of HD	<p>AIM: To describe pharmacokinetics of lacosamide in participants with renal impairment and ESRD (including hemodialysis)</p> <p>RESULTS: Positive correlation found between renal function (CrCl) and total clearance of lacosamide (CL/F)</p> <p>Mean plasma concentration of lacosamide after single dose trended higher in patients with renal impairment (mild: 2.95 mg/L, moderate: 3.06, severe: 3.02) than healthy volunteers (2.69). Highest plasma concentrations found in severe renal impairment</p> <p>Total clearance was lower Group 4 (1.34 L/h) compared with Group 1 (2.13 L/h); mean $t_{1/2}$ was higher in Group 5 (18.3 h) compared with Group 1 (13.2 h)</p> <p>Plasma concentration of lacosamide decreased after HD—starting at 2.19 mg/L on dialysis-free day and reaching at end of HD mean 0.89 mg/L</p> <p>Authors conclude that dose adjustment is not needed in mild-moderate renal impairment, but is needed in severe renal impairment and ESRD (recommend max 250 mg/day), and that the decreased systemic lacosamide exposure in HD necessitates dose supplementation up to 50%</p>	NR

Table 1 (continued)

Author, year of publication	Study design	Population studied (seizure types)	N	Age, years Range (average \pm SD)	Sex male <i>n</i> (%)	Lacosamide dosage range	Study aim and main results	Suggested reference range
Franquiz et al., 2018 [45]	Case report	Adult (status epilepticus)	1	60 (NA)	M	200 mg IV infusion over 30 min BID	AIM: To report the pharmacokinetics of lacosamide in a critically ill male receiving CVVH. RESULTS: Lacosamide peak concentration at steady state: 7.7 mg/L and trough: 5.9 mg/L (plasma sampled from prefilter port before addition of replacement fluid) which was within target range. Authors suggest dosing for patients undergoing CVVH can be the same as dosing in patients with normal renal function	5–12 mg/L
Wieruszewski et al., 2018 [46]	Case report	Adult (nonconvulsive status epilepticus)	1	78	M	400 mg IV LD then 200 mg IV BID maintenance	AIM: To report lacosamide pharmacokinetics in a critically ill male with adequate liver function undergoing CVVH RESULTS: C_{max} at steady state was 7.4 mg/L, which was therapeutic, but C_{min} fell below recommended reference range. Vd: 0.69 L/kg, (compared with Vd of 0.60 L/kg expected in healthy individuals), which may be due to increased effective total body volume from CVVH CL was 3.07 L/h (compared with CL of 2.55 L/h expected in healthy individuals), demonstrating that CVVH is able to clear lacosamide	5–10 mg/L

Table 1 (continued)

Author, year of publication	Study design	Population studied (seizure types)	N	Age, years Range (average \pm SD)	Sex male <i>n</i> (%)	Lacosamide dosage range	Study aim and main results	Suggested reference range
<i>Older adults</i>								
Cawello and Schaefer, 2014 [48]	Post hoc analysis (data from double-blind, placebo-controlled, multiple dose, parallel group study (SP620))	Healthy volunteers	35 Young males: 12 Elderly females: 12 Elderly males: 11	Young males: (36.8) Elderly males (71.3) Elderly females (69.7)	65.7	100 mg single dose on day 1, then 100 mg BID for 4.5 days	AIM: To develop equations that predict lacosamide pharmacokinetics with one steady-state serum concentration and validate them with lacosamide serum concentrations of healthy individuals RESULTS: Mean $C_{\max(ss)}$ for elderly females was 7.40 ± 0.92 , for elderly males was 6.31 ± 1.2 , and for young males was 4.84 ± 0.47 mg/L. Approximated (with equations) was 6.62 ± 0.92 , 6.01 ± 1.36 , and 4.45 ± 0.69 mg/L, respectively. Values were slightly underestimated Mean trough concentration at steady state for elderly females was 3.72 ± 0.73 , elderly males was 3.57 ± 0.95 , and young males was 2.44 ± 0.43 mg/L. Approximated was 3.82 ± 0.53 , 3.46 ± 0.79 , and 2.57 ± 0.40 mg/L, respectively. Values were slightly overestimated Mean AUC at steady state ($\text{mg}^{\cdot}\text{h/L}$) for elderly females was 62.5 ± 8.46 , for elderly males was 56.0 ± 12.36 , and young males was 41.6 ± 5.64 . Approximated was 62.0 ± 8.62 , 56.3 ± 12.78 , and 41.7 ± 6.44 , respectively Sex and age had no effect on mean $C_{\max(ss)}$ and $C_{\text{trough}(ss)}$ and AUC $_{(ss)}$	NR
Markoula et al., 2014 [30]	Retrospective observational	Adult patients (simple or complex focal)	128	19–66 Median: 39	47.7	50–600 mg/day	AIM: To investigate impact of sex, age, dose, and concomitant AEDs on lacosamide serum concentrations RESULTS: Mean lacosamide serum concentration: 31.4 ± 19.5 $\mu\text{mol/L}$ (range 1–98) Women had significantly higher mean lacosamide concentrations compared with men (37.2 ± 23.6 vs 26.8 ± 12.9 $\mu\text{mol/L}$, $p=0.001$), which authors suggest was due to lower mean body weight in women No effect of age on lacosamide serum concentration was found. Lacosamide serum concentration was dose-dependent Patients on concomitant enzyme-inducing AEDs (such as carbamazepine or phenytoin) had significantly lower lacosamide concentrations than those taking lacosamide as monotherapy (23.5 ± 11.0 vs 32.7 ± 17.9 $\mu\text{mol/L}$, $P < 0.002$). Valproic acid had no significant effect on lacosamide serum concentrations.	NR

Table 1 (continued)

Author, year of publication	Study design	Population studied (seizure types)	N	Age, years Range (average \pm SD)	Sex male n (%)	Lacosamide dosage range	Study aim and main results	Suggested reference range
Schaefer et al., 2015 [49]	Post hoc analysis (from 2 phase I and 2 phase III trials)	Healthy subjects, and adults with focal epilepsy	66 healthy subjects 565 adults with focal epilepsy	Healthy: 18–40 Elderly females > 65 (69.7 \pm 4.1) Elderly males > 65 (70.9 \pm 6.9) Young females 18–40 (30.1 \pm 5.0) Young males 18–45 (36.8 \pm 6.4) Epileptic: 16–71 (female: 37.6 \pm 12.2; male: 37.4 \pm 12.3)	35.8 50.8	200 mg PO BID 100 mg PO on day 1, 100 mg BID on days 4–7, 100 mg on day 8 200, 400, or 600 mg PO daily	AIM: To investigate the influence of age and sex on lacosamide pharmacokinetics RESULTS: Healthy subjects: Younger individuals had lower $C_{max(ss)}$ and AUC, and higher CL/F values than older, but scaling by body weight or Vd reduced the difference in exposure Females had higher $C_{max(ss)}$ than males, but again the difference decreased with scaling by body weight Young males had a lower $C_{max(ss)}$ (4.8 mg/L) than the other groups (Elderly females: 7.4, elderly males: 6.2, Young females: 6.8). In addition, they had a higher CL/F (2.42 L/h) (Elderly females: 1.61, elderly males: 1.84, young females 1.79) Adults with epilepsy: Age, BMI, CrCl and ethnicity did not have statistical effect on lacosamide pharmacokinetics. Simulations demonstrated that weight had < 15% difference on lacosamide plasma concentrations Authors concluded that age and sex have minimal effects on lacosamide plasma concentration after applying a main scaling factor for body weight or Vd	NR
<i>Pediatrics</i> Burns et al., 2019 [53]	Retrospective observational	Children with epilepsy from Norway and Denmark (focal or multifocal)	124	2–17 (median 15)	50.8	50–600 mean \pm SD: 283 \pm 114	AIM: To describe the effect of age, dose, sex, comedication, and duration of treatment on lacosamide pharmacokinetics in children RESULTS 94% of patients had serum concentrations in reference range (9–40 μ mol/L) C/D ratio was significantly higher in age group 13–17 years than age groups of 6–12 years and < 6 years No statistically significant difference in C/D ratio between girls and boys Higher serum concentrations were seen in patients who continued on lacosamide for > 1 year	Norway: 10–40 μ mol/L (3–10 mg/L) Denmark: 9–35 μ mol/L (2.25–8.75 mg/L)

Table 1 (continued)

Author, year of publication	Study design	Population studied (seizure types)	N	Age, years Range (average \pm SD)	Sex male <i>n</i> (%)	Lacosamide dosage range	Study aim and main results	Suggested reference range
Martin et al., 2018 [55]	Conference abstract (post hoc analysis)	Children with epilepsy (unspecified seizure type)	NR	NR	NR	NR	<p>AIM: To develop a population pharmacokinetic model for lacosamide dosing in children to ensure comparable exposure between children and adults</p> <p>RESULTS: Lacosamide with valproate increased lacosamide AUC by 14% (90% CI 7–22%) and with inducer AEDs decreased AUC by 17% (90% CI 12–22%) In children <2 years, CL was higher than predicted from allometric theory (not attributed to race, sex, or eGFR)</p> <p>Authors conclude that concomitant AEDs have little impact on lacosamide AUC, therefore children have comparable exposure to lacosamide as adults</p>	NR
Kronenfeld et al., 2019 [54]	Conference abstract (retrospective observational)	Children with refractory epilepsy (unspecified seizure type)	22	3–18 (11 \pm 4)	NR	6.6–11 mg/kg	<p>AIM: To investigate the utility of TDM of lacosamide in children</p> <p>RESULTS: Median plasma concentration of lacosamide was 7.1 mg/L and ranged from 5.9 to 11.9 mg/L In 21.4% of children with plasma concentrations <10 mg/L, there was no change in frequency of seizures In 40% of children, they had a reduction of seizure frequency with lacosamide plasma concentrations of >10 mg/L</p>	10–20 μ g/mL
Winkler et al., 2018 [56]	Post hoc analysis (from 2 early-phase clinical trials)	Pediatric patients with epilepsy (unspecified seizure type)	79	1 month–17 years	47	2 mg/kg/day–12 mg/kg/day oral solution	<p>AIM: To create a population pharmacokinetic model for lacosamide used in pediatrics</p> <p>RESULTS: Lacosamide clearance in pediatrics increased (+53.5%) with concomitant inducer AED, resulting in a 35% lower AUC^(ss) Age, race, sex, eGFR, and concomitant valproic acid had no effect on lacosamide clearance</p>	NR

Table 1 (continued)

Author, year of publication	Study design	Population studied (seizure types)	N	Age, years Range (average \pm SD)	Sex male <i>n</i> (%)	Lacosamide dosage range	Study aim and main results	Suggested reference range
Winkler et al., 2019 [57]	Pharmacokinetic model and simulation of 2 previous trials in children (secondary analysis)	Children with epilepsy and healthy adults	79 children 43 adults	Children: <2 to <18 years Adults: 18–45 years	NR	<20 kg: 12 mg/kg/day 20–<30 kg: 10 mg/kg/day 30–<50 kg: 8 mg/kg/day \geq 50 kg: 400 mg/day Administered IV (duration 15–60 min) BID	AIM: To develop a population pharmacokinetic model for children receiving IV lacosamide using a two-compartment model and compare it to pharmacokinetics of IV lacosamide in healthy adults RESULTS: In the group of \geq 50 kg, as body weight increased, C_{max} and AUC decreased Median $C_{max(ss)}$ was predicted to be 9–21% higher at the end of a 15-min IV infusion compared with oral administration Median $C_{max(ss)}$ was predicted to be only 2–10% higher at the end of a 60-min IV infusion compared with oral administration AUC values were comparable between PO and IV administration, and not dependent on infusion duration	NR
<i>Race</i>								
Bautista et al., 2012 [58]	Conference abstract (retrospective observational)	Patients with epilepsy	19 (10 Caucasian, 9 African American)	African American: 21–50 (34.2) Caucasian: 18–49 (34.3)	52.6	African American: mean 390 mg Caucasian: mean 260 mg	AIM: To compare lacosamide pharmacokinetics between African Americans and Caucasians RESULTS: In patients taking 200 mg/day, mean lacosamide concentration was 4.07 mg/L for African American and 4.72 mg/L for Caucasian and in 400 mg/day, mean concentration was 5.94 mg/L for African American and 9.00 mg/L for Caucasian Authors conclude that African American patients seem to have lower lacosamide serum concentrations compared to Caucasian patients, although not statistically significant	NR
Hong et al., 2016 [59]	Randomized, double-blind, placebo-controlled trial	Chinese and Japanese adults (focal)	547	Range not reported (32.5 \pm 12.0)	54.8	200–400 mg PO	AIM: To investigate efficacy, safety, and tolerability of lacosamide in Asian patients. RESULTS: Median change in seizure frequency/28d for placebo, lacosamide 200 mg/d and 400 mg/d was –1.22 (–93.0 to 39.8), –3.33 (–754.3 to 165.2), and –4.50 (–97.5 to 28.2), respectively. Both lacosamide groups were significantly different from placebo Mean lacosamide plasma concentration at end of titration period in 200 mg/d was 5.248 mg/L, and in 400 mg/d was 10.032 mg/L. Plasma concentrations were stable during maintenance period Lacosamide plasma concentrations did not appear related to sex after normalizing for body weight and dose	NR

Table 1 (continued)

Author, year of publication	Study design	Population studied (seizure types)	N	Age, years Range (average \pm SD)	Sex male <i>n</i> (%)	Lacosamide dosage range	Study aim and main results	Suggested reference range
Kim et al., 2012 [61]	Double-blind randomized controlled trial	Healthy Korean volunteers	49	(27.4 \pm 5.7)	100	50–200 mg PO (BID for multiple dose groups)	<p>AIM: To investigate the pharmacokinetics of single-dose and multiple dose lacosamide in healthy Korean volunteers and compare its pharmacokinetics in Caucasian populations</p> <p>RESULTS: After a single dose, for group A, B, and C, lacosamide C_{max} geometric mean (%CV) was 1.63 \pm 9.1, 2.85 \pm 14.6, and 5.84 \pm 24.3 mg/L, respectively. After multiple doses, for groups B and C, C_{max} geometric mean (%CV) was 6.23 \pm 15.0 and 13.13 \pm 8.9 mg/L, respectively. When normalized by dose and weight, C_{max} and AUC across treatment groups were similar C_{max} and AUC were dose proportional for both single and multiple dose, but lacosamide 50 mg x1 resulted in C_{max} slightly higher than proportional AUC was increased in Koreans compared to Caucasians (possibly due to decreased body weight and height)</p>	NR
Mahulikar et al., 2018 [51]	Conference abstract (retrospective observational)	Patients with epilepsy	132 sera	19–71 (41.3)	40 (sera)	25–1,000 mg/day Median: 345.37 mg/kg	<p>AIM: To investigate the impact of race on AED concentrations, including lacosamide</p> <p>RESULTS: Mean serum concentrations of lacosamide was 7.21 mg/L Age and sex had no effect on lacosamide serum concentrations African American patients had significantly lower lacosamide serum concentrations ($p=0.007$) and had a weaker correlation between daily dose and serum concentrations ($r=0.042$ compared with $r=0.47$ for Caucasians), therefore may require higher doses Enzyme-inducer AEDs resulted in decreased serum concentrations of lacosamide</p>	NR
Yamamoto et al., 2019 [60]	Conference abstract (retrospective observational)	Patients with epilepsy	430	1–91	NR	NR	<p>AIM: To investigate interactions between AEDs and lacosamide in Japanese patients</p> <p>RESULTS: The C/D ratio was significantly lower in patients on concomitant enzyme-inducer AEDs than those who were not. Authors conclude that TDM is a useful tool to determine the extent of drug interactions in patients on multiple AEDs</p>	NR

Table 1 (continued)

Author, year of publication	Study design	Population studied (seizure types)	N	Age, years Range (average \pm SD)	Sex male <i>n</i> (%)	Lacosamide dosage range	Study aim and main results	Suggested reference range
<i>Critically ill</i>								
Ramsay et al., 2015 [50]	Retrospective observational	Patients with refractory SE treated with lacosamide in the ICU	51	16–83		400 mg IV	<p>AIM: To investigate efficacy of weight-based dosing of a loading dose of lacosamide in the ICU</p> <p>RESULTS: Lacosamide concentration in reference range was attained most consistently in patients receiving an LD of 10–12 mg/kg at an infusion rate of 0.4 mg/kg/min. There was much variation in blood concentrations based on lacosamide LD (mg/kg) but is generally dose proportional.</p> <p>No difference across age groups in plasma concentrations based on weight-based dosing.</p> <p>Authors conclude that weight-based dosing of lacosamide should be employed to ensure therapeutic blood concentrations.</p>	15–20 mg/L
<i>Overdose reports/toxicity</i>								
Berei et al., 2018 [67]	Case report	Inpatient (generalized tonic-clonic)	1	70	F	200 mg IV initial dose, then 300 mg IV q12h	<p>AIM: To describe an incidence of life-threatening ventricular tachycardia associated with administration of lacosamide.</p> <p>RESULTS: Patient with history significant for valvulopathy admitted to hospital for chest pain, then after experiencing tonic-clonic seizures in hospital, was started on IV levetiracetam, IV lacosamide, and IV phenytoin. Approximately 2 days after starting lacosamide, lacosamide serum concentration was 12.4 mg/L.</p> <p>Patient experienced monomorphic ventricular tachycardia about 2 h after second lacosamide dose. This happened again 2 h after the next lacosamide dose, after which lacosamide was discontinued (notably, patient was not on any QTc-prolonging agents, and Mg²⁺ and K⁺ concentrations were normal.)</p> <p>Naranjo Adverse Drug Reaction Scale suggests a 'probable' relationship between lacosamide and ventricular tachycardia.</p>	1–15 mg/L

Table 1 (continued)

Author, year of publication	Study design	Population studied (seizure types)	N	Age, years Range (average \pm SD)	Sex male <i>n</i> (%)	Lacosamide dosage range	Study aim and main results	Suggested reference range
Deslandes et al., 2015 [68]	Case report	Caucasian patient (atypical left temporal lobe epilepsy)	1	26	M	6,000 mg (suicide attempt)	<p>AIM: To describe the toxicity and concentrations of lacosamide in a suicide attempt</p> <p>RESULTS: After supposed ingestion of lacosamide (and lamotrigine) in an attempted suicide, peak lacosamide concentration was 44.5 mg/L at 10 h post ingestion. Lacosamide concentration reached reference range after 70 h</p> <p>Overdose of lacosamide and lamotrigine resulted in tonic-clonic seizure (paradoxical proconvulsant effect). Patient also experienced elevated CK, but otherwise normal renal function</p>	NR
Kierman et al., 2019 [69]	Case report	Patient with epilepsied seizure type)	1	61	F	NR	<p>AIM: To describe a case of lacosamide toxicity which was remedied through use of HD</p> <p>RESULTS: The patient intentionally ingested a 'handful' of lacosamide 200 mg tablets and presented to the emergency department with a plasma concentration of 50.3 mg/L, altered mental status and abnormal ECG results (including prolonged PR interval)</p> <p>HD started 10 h post ingestion resulted in baseline ECG and mental status</p>	6.6–18.3 mg/L

Table 1 (continued)

Author, year of publication	Study design	Population studied (seizure types)	N	Age, years Range (average \pm SD)	Sex male n (%)	Lacosamide dosage range	Study aim and main results	Suggested reference range
<i>Other</i>								
Kropeit et al., 2015 [5]	Randomized, double-blind, positive- and placebo-controlled trial	Healthy volunteers	220	(24.7 \pm 6.6)	45.3	200 mg BID–400 mg BID	<p>AIM: To establish the effect of lacosamide on the QTc interval and other ECG parameters.</p> <p>RESULTS:</p> <p>QTc interval was affected by -4.3 ms (400 mg/day) and -6.3 ms (800 mg/day), but the upper range of the CI were below the $+10$ ms non-inferiority margin, so increase was not significant. Lacosamide plasma concentration did not affect QTc.</p> <p>Increase in HR versus placebo in lacosamide 800 mg/day, but this increase was not seen in lacosamide 400 mg/day.</p> <p>Lacosamide had no effect on QRS duration</p> <p>Lacosamide resulted in dose-related changes in PR interval. Placebo increase in PR: 6.3, 400 mg/day: 13.6, 800 mg/day: 18.2 ms. However, Pearson coefficient = 0.14. Due to flat relationship, likely wide margin of safety.</p> <p>Mean plasma concentration at steady state of lacosamide was dose proportional. (400 mg/day: 10.9 mg/L; 800 mg/day: 21.3 mg/L)</p> <p>Normalization of $C_{max(ss)}$ and $AUC_{(ss)}$ by dose and body weight resulted in similar values between sexes</p>	NR
Landmark et al., 2018 [66]	Conference abstract (retrospective)	Patients using lacosamide	75 with ID, 148 without ID (total $n = 223$)	With ID: 4–68 (median 28)	50.7 (with ID)	ID: 323 mg/day No ID: 328 mg/day	<p>AIM: To compare lacosamide concentrations and efficacy in patients with and without intellectual disabilities (ID)</p> <p>RESULTS:</p> <p>Overall, 70% of patients had improved seizure control AEs were seen in 36% of patients with ID and 51% in patients without (mostly mild)</p> <p>Lacosamide serum concentration in both groups was 22 mmol/L and concentration/dose (C/D)-ratio was 0.07 in patients with ID and 0.06 in those without, *demonstrating 5–6-fold pharmacokinetic variability*</p>	NR

AE adverse effect, AED antiepileptic drugs, AUC area under the concentration–time curve, $AUC(ss)$ area under the concentration–time curve at steady state, BID twice daily, BMI body mass index, C/D ratio concentration–dose ratio, CK creatine kinase, CL drug clearance, CL/F apparent oral clearance, C_{max} peak drug concentration, $C_{max(ss)}$ peak drug concentration at steady state, CSF cerebrospinal fluid, $C_{trough(ss)}$ trough drug concentration, $C_{trough(ss)}$ trough drug concentration at steady state, CrCL creatinine clearance, CVVH continuous venovenous hemofiltration, EE ethinyl estradiol, eGFR glomerular filtration rate, E_{max} the maximum effect attributable to the drug, ESRD end-stage renal disease, HD hemodialysis, ICU intensive care unit, ID intellectual disabilities, ITT intention to treat, IV intravenous, LD loading dose, N/A not applicable, NR not reported, OC oral contraceptives, PO oral, SC subcutaneous, SE status epilepticus, RID relative infant dose, TEAE treatment-emergent adverse event, TID three times daily, TDM therapeutic drug monitoring, t_{max} time it takes for the drug to reach maximum drug concentration

that crosses the blood–brain barrier and enters the central nervous system (CNS) because the CNS is where it exerts its mechanism of action to prevent seizures. Both studies found that both mean plasma and mean CSF concentrations were dose proportional, and there was a linear relationship between plasma and CSF concentrations. However, Michelhaugh et al. only saw this positive correlation in patients on lacosamide as ongoing treatment, and not in lacosamide-naïve patients [23]. In patients on lacosamide therapy as maintenance, the dose proportionality proves that lacosamide serum concentration at steady state is an appropriate surrogate for CSF concentration.

Because of the multiple studies that have demonstrated a linear relationship between lacosamide dose and plasma concentrations, it is clear that TDM may be a practical approach to ensure plasma concentrations are within a reference range, once established, in certain populations. However, there is some disagreement on dose–response and adverse reaction proportionality. Several RCTs found increased adverse reactions with increasing dosages of lacosamide [10], but a smaller observational study failed to find a correlation between lacosamide plasma concentration and adverse effects [17]. The latter study was composed of a small sample size of 70 participants, so they may not have been adequately powered to detect a correlation, which may explain the difference in results compared with the RCTs. Overall, more research is needed to develop a well-established reference range for lacosamide TDM, as there is currently some variability in suggested reference ranges. Despite the present limitations in the use of TDM for lacosamide, including lack of a defined reference range, there is likely a place for it in clinical practice in specific populations with altered pharmacokinetics, which will be explored further in this discussion.

4.1 Drug–Drug Interactions

One factor that may make TDM desirable in clinical practice is the presence of unpredictable or significant drug interactions. Drug interactions may occur at any stage of the drug's passage through the body, including absorption, distribution, metabolism, and excretion. Several older AEDs have many clinically important drug interactions because they are liver microsomal enzyme inducers or inhibitors, resulting in low or high concentrations, respectively, of the interacting medication. Although lacosamide does not act as a clinically significant enzyme inducer or inhibitor, it is metabolized by CYP 3A4, 2C9, and 2C19, so there is a potential for significant drug–drug interactions [1, 6].

As AEDs are often used in combination when patients do not attain seizure freedom with monotherapy, there have been multiple studies assessing for interactions between lacosamide and other AEDs. Two studies in healthy

volunteers looked at combining lacosamide with valproic acid [24] and carbamazepine [25], which influence liver microsomal enzymes by inhibition and induction, respectively. The authors in both studies found that neither the pharmacokinetics of lacosamide were affected by either AED, nor were the pharmacokinetics of valproic acid or carbamazepine influenced by lacosamide coadministration. Similarly, other trials have demonstrated that the pharmacokinetics of lacosamide generally do not seem to be affected by coadministration with other AEDs [4, 10, 22, 25, 26]. On the other hand, in a retrospective observational study with 973 patients with epilepsy, May et al. found that coadministration with an enzyme-inducer AED resulted in a 30–40% decrease in lacosamide trough plasma concentrations, with a larger effect when more than one enzyme-inducer AED was coadministered with lacosamide [28]. However, there was no significant effect of enzyme-inhibitor AEDs on lacosamide trough concentrations, which is consistent with the other reported studies. Likewise, four other studies found a decreased concentration–dose ratio with lacosamide and concomitant enzyme-inducer AEDs compared with lacosamide monotherapy [15, 28–30]. In addition to the pharmacokinetic interactions, pharmacodynamic interactions between lacosamide and other sodium-channel blocking AEDs such as carbamazepine, lamotrigine, and phenytoin, have been reported. Novy et al. described such interaction in a case series of seven patients. Lacosamide doses were standard and plasma concentrations ranged from 1.3 to 12 mg/L [32]. The authors of this study concluded that the patients described, although having lacosamide concentrations within or slightly below the suggested reference range, had increased CNS adverse effects. A study by Hillenbrand et al. had similar findings, in which patients on lacosamide with a concomitant sodium channel blocker AED had a significantly increased incidence of dizziness [17]. Taken together, this suggests the possibility of a pharmacodynamic interaction between lacosamide and other sodium channel blocking AEDs, resulting in an increase in adverse effects, so should be used together cautiously.

Lacosamide has also been studied in combination with several other commonly used medications to assess for drug–drug interactions. Administration of lacosamide with oral contraceptives, omeprazole, or digoxin have been found not to result in any clinically significant drug interaction or concentration changes [33–35]. Notably, all of these studies were conducted in healthy volunteers, which may not necessarily be generalizable to patients on medications for epilepsy.

Overall, lacosamide has few drug–drug interactions and typically exhibits predictable pharmacokinetics. Digoxin, oral contraceptives, omeprazole, and enzyme-inhibiting AEDs have all shown to have no significant effect on efficacy or pharmacokinetics of lacosamide when coadministered

with lacosamide. However, there is some disagreement on whether enzyme-inducing AEDs impact the pharmacokinetics of lacosamide, with several studies finding no effect, and other studies finding a significant effect. Because several studies did find a decrease in lacosamide plasma concentrations when given concomitantly with enzyme-inducing AEDs, TDM may be of benefit to monitor this and ensure lacosamide concentrations do not drop drastically when an interacting AED is added on.

4.2 Drug Formulations

An advantage that lacosamide has over other AEDs is that it is available in an IV formulation, which is important for emergent treatment of seizures, such as in status epilepticus, or in situations where oral administration is not feasible for a patient. Because lacosamide has near 100% bioavailability, the doses of lacosamide in IV versus oral administration are similar [6]. Multiple studies have evaluated the safety, efficacy, and pharmacokinetics of IV lacosamide compared with oral lacosamide, and have shown that IV lacosamide is equally efficacious and tolerable [6, 35–38]. Bioequivalence of IV and oral lacosamide was demonstrated in a study in healthy volunteers by Cawello et al. [37]. As in oral lacosamide, IV lacosamide administration resulted in a linear relationship between dose and plasma concentration; maximum mean concentration immediately following IV administration was approximately 6 mg/L for 200 mg of lacosamide, 9 mg/L for 300 mg of lacosamide, and 12 mg/L for 400 mg of lacosamide [38]. This shows that a single IV loading dose of lacosamide results in similar plasma concentrations to equivalent oral daily doses at steady state, which was also demonstrated through simulations by Cawello and Andreas [40].

In addition to IV formulation of lacosamide, other formulations of lacosamide have been used in studies, including an oral syrup and a subcutaneous injection. Cawello et al. compared the bioavailability and pharmacokinetics of lacosamide in an oral tablet versus oral syrup in a randomized, open-label crossover trial [21]. The tablet and syrup demonstrated bioequivalence, with similar mean time for the drug to reach maximum drug concentration (t_{\max}), C_{\max} , and AUCs. In a case report by Remi et al., the authors described a palliative male patient who lost the ability to swallow, and a subcutaneous injection was preferred to an IV injection [41]. This patient was previously on lacosamide 400 mg/day and was switched to off-label subcutaneous lacosamide at a dose of 200 mg undiluted IV solution for two doses. No seizures were experienced during the time of the subcutaneous injections, indicating apparent efficacy of lacosamide. Serum lacosamide concentration immediately prior to the subcutaneous injection was 3.56 mg/L, peak

lacosamide concentration (50 min after subcutaneous dose) was 5.44 mg/L, and trough concentration was 3.67 mg/L.

One advantage of lacosamide is the availability of an IV formulation, which has been found to be bioequivalent to the tablet. Oral syrup and subcutaneous formulation may also be of benefit when choosing among antiepileptic drugs.

4.3 Pregnancy

It is known that physiological changes due to pregnancy result in altered pharmacokinetics of drugs including increased renal clearance, altered hepatic metabolism, and increased volume of distribution, among other changes [42]. Lacosamide pharmacokinetics are susceptible to these physiological changes during pregnancy since it undergoes both hepatic metabolism and renal excretion. There are limited studies that have assessed the use of lacosamide in pregnancy, and currently the drug monograph relies on animal studies to provide a recommendation [1]. In particular, there is very limited evidence on the effect of pregnancy status on lacosamide plasma concentrations. Only one study analyzing lacosamide plasma concentrations in pregnancy was identified [43]. Ylikotila et al. describe a case report of a woman with focal secondarily generalized seizures who started lacosamide in her eighth week of pregnancy. The child born at 36 weeks had no malformations. Measured lacosamide concentrations in the mother and cord blood immediately after delivery were 3.8 ± 1.1 mg/L and 3.9 ± 1.2 mg/L, respectively, demonstrating that lacosamide must freely cross the placenta. Based on lacosamide concentrations drawn from breast milk 5 days postpartum and the child 8 days postpartum, they estimated a relative infant dose (RID) of 1.8%. An RID of < 10% is generally considered to have minimal clinical impact on infants [44].

Currently, more evidence is needed on whether lacosamide kinetics are altered in pregnancy. Because lacosamide dosage requirements may change during pregnancy, and it is vital for the mother to remain seizure free in pregnancy to avoid harm to the fetus, TDM may be of benefit to monitor lacosamide plasma concentrations.

4.4 Renal Impairment

Renal function is an important consideration for many medications, as many require dose adjustments with decreasing renal function, and some may be contraindicated below a certain concentration of renal function. Medications that are renally eliminated, such as lacosamide, may build up in the body with declining renal function, and have the potential to cause toxicity. One way to ensure a drug is not building up to a toxic concentration is through use of TDM. Cawello et al. demonstrated that as renal function declines, plasma concentration of lacosamide increases due to a decrease in renal

clearance [7]. To illustrate, clearance of lacosamide was 2.13 L/h in healthy volunteers, 1.74 L/h in moderate renal impairment, and 1.34 L/h in severe renal impairment. A decrease in maximum daily dose of lacosamide to 250–300 mg/day (compared with the typical 400 mg/day) was recommended in adults with severe renal impairment and end-stage renal disease, but not mild or moderate renal impairment.

Renal replacement therapy has the potential to significantly remove lacosamide due to the characteristics of lacosamide including small molecular weight, low protein binding [7], 40% renal elimination [6], and small volume of distribution. Two case reports have examined lacosamide use in continuous venovenous hemofiltration (CVVH) in critically ill patients [45, 46]. In both cases, C_{\max} at steady state was around 7 mg/L, but in the case study by Wieruszewski et al., they found that the minimum drug concentration (C_{\min}) fell below the reference range [46]. Although the authors recommended dosing of lacosamide as in normal kidney function, they suggest that use of TDM may be warranted to ensure concentrations within a suggested reference range of 5–12 mg/L. On the other hand, Cawello et al. found that in patients on hemodialysis, systemic exposure of lacosamide was significantly decreased, so they may require dose supplementation of up to 50% to maintain concentrations within a reference range [7].

Due to the limited data on the use of lacosamide in patients with renal dysfunction or on renal replacement therapy, and small sample sizes of available studies, more evidence is required to form a clear recommendation regarding pharmacokinetic changes of lacosamide in renal dysfunction and renal replacement therapy. Because current data suggest that lacosamide plasma concentrations may increase in severe renal impairment and systemic exposure is decreased with hemodialysis, TDM may be useful to monitor lacosamide plasma concentrations of such patients.

4.5 Older Adults

A variety of factors change as people age, including body composition and presence of comorbidities, with both affecting the pharmacokinetics of medications. Older adults generally have higher relative lipid content and lower total body water, which affect drug distribution, and may have decreased renal and hepatic clearance [47]. There are several studies investigating the pharmacokinetic changes of lacosamide in an older population, and generally they have found that age in itself does not have a significant effect on lacosamide plasma concentrations [29, 47–50]. To illustrate, in a post hoc analysis including both healthy subjects and patients with epilepsy, Schafer et al. found that although younger subjects had lower C_{\max} at steady state (4.8 mg/L vs 6.2 mg/L), AUC, and higher clearance than older subjects, there was no significant difference when body weight

or volume of distribution was adjusted for [49]. However, several of the studies that found no effect of age on lacosamide pharmacokinetics were fairly small, so they may not have been powered to show a difference. In contrast, a large retrospective analysis by May et al. found that adults aged > 60 years had 20% higher lacosamide serum trough concentrations than those aged < 60 years, suggesting the need for dose reduction in older adults [28].

Although currently the majority of studies have not found any impact of age on lacosamide concentrations and thus recommend standard dosing, one study suggests that older adults may require lower dosing to prevent accumulation of lacosamide. It may be beneficial to monitor lacosamide plasma concentrations in older adults periodically to ensure stable concentrations and prevent toxicity.

4.6 Pediatrics

Children have substantially different physiological characteristics from adults, and these characteristics change throughout the life of a child. For example, stomach pH varies, which alters absorption of medications; total body water is higher than in adults, which alters volume of distribution; and drug metabolism varies throughout pediatric age groups [52]. Because of these changes, drug pharmacokinetics in pediatrics is often much different from that in adults. Lacosamide is currently approved as an antiepileptic in children aged ≥ 4 years in the European Union [2], but is not approved for pediatric use in Canada [1]. The current literature on the pharmacokinetics of lacosamide in pediatric populations is limited. A recent retrospective observational study examined the effect of age, dose, sex, and duration of treatment on lacosamide pharmacokinetics in children [53]. The only significant factor on lacosamide concentrations (normalized by dose) was age; children aged between 13 and 17 years had significantly higher concentration–dose ratios than children aged between 6 and 12 years and children aged < 6 years. Another study investigated the utility of TDM of lacosamide in children and found that lacosamide was more effective when the plasma concentration was > 10 mg/L [54].

Four studies examined the use of lacosamide with concomitant AEDs and the effect on pharmacokinetics in pediatrics [28, 53, 55, 56]. Martin et al. described lacosamide use with concomitant AEDs, and found that AUC was increased by 14% with coadministration of valproate, and decreased by 17% with coadministration of enzyme-inducer AEDs [55]. However, the authors acknowledge that this change is small, and children likely have similar exposure as in adults. Similarly, Burns et al. found no effect of enzyme-inducer AEDs on lacosamide pharmacokinetics in children, although their sample size was small ($n = 3$) [53]. In contrast, in a secondary analysis, Winkler et al. examined lacosamide use in

pediatrics, and found that lacosamide clearance increased by about 53% when administered with a concomitant enzyme-inducer AED [56]. May et al. found a similar reduction of AUC of 46% when children were given concomitant enzyme-inducer AEDs compared with monotherapy [28].

In a secondary analysis and simulation of 2 previous trials in children, Winkler et al. compared the pharmacokinetics of IV and oral lacosamide in children with epilepsy with that in healthy adults [57]. They demonstrated that the AUC in pediatrics of oral and IV lacosamide was comparable, so the weight-based dosing used for oral lacosamide can likely be applied to IV lacosamide.

Currently, lacosamide pharmacokinetics in children compared with adults is not well elucidated. There is some disagreement on the extent of the impact of enzyme-inducer AEDs in pediatrics, as seen in adults. A simulation found that lacosamide exposure was similar with IV and oral administration, so can be dosed similarly. There is currently a lack of definitive evidence regarding TDM of lacosamide in pediatrics, so at this point it is unknown whether TDM would be useful in this population. Further studies are needed.

4.7 Race

The pharmacokinetics of lacosamide has been compared among various races in multiple studies, including Caucasian, African-American, Korean, Chinese, and Japanese. Two conference abstracts of retrospective observational studies described lacosamide pharmacokinetics in African-Americans compared with Caucasians [51, 58]. Both studies concluded that lacosamide serum concentrations seem to be lower in African-American people than in Caucasian people. For example, in their small study of 19 participants, Basha et al. found that serum concentrations were comparable between the two groups at a dose of 200 mg/day; however, at a dose of 400 mg/day, mean lacosamide concentration of African-American participants was 5.94 mg/L, and Caucasian participants was 9.00 mg/L [58]. While this difference was not statistically significant, it may suggest that African-American people require higher doses of lacosamide to maintain a plasma concentration similar to that of Caucasian people.

A randomized controlled trial by Hong et al. investigated the safety and efficacy of lacosamide in an Asian population, including Chinese and Japanese people, which was a population that had not been previously studied [59]. While this study did not directly compare Asian to Caucasian people, they found similar mean plasma concentrations and dose proportionality of lacosamide to what has typically been seen in studies of Caucasian populations; about 5 mg/L at a dose of 200 mg/day and 10 mg/L at a dose of 400 mg/day. Another study found a significant interaction between

enzyme-inducer AEDs and lacosamide in Japanese patients, which is similar to that seen in previous studies in Caucasians [60]. In contrast, Kim et al. compared lacosamide pharmacokinetics in Korean and Caucasian people and found a relatively increased AUC of lacosamide in Korean people [61]. However, this was likely due to a lower mean body weight and height in the Korean participants compared with Caucasian people.

Overall, the pharmacokinetics of lacosamide are likely comparable between Asian and Caucasian populations, especially when difference in mean body weight is accounted for. However, based on the limited studies available, lacosamide administration to African-American people may result in lower plasma concentrations compared with Caucasian people. Because of this, TDM may be necessary in African-American people to ensure plasma concentrations within a reference range and increase the likelihood of seizure prevention. Regardless, further studies are needed.

4.8 Critical Illness

Critical illness involves multisystem dysfunction (including respiratory, neurological, and cardiovascular problems), is life-threatening for patients and requires admission to an intensive care unit (ICU) for management. There are many considerations involved regarding the pharmacokinetics of medications in these patients, including medications specific to their illness causing drug interactions, changes in blood flow from the periphery to core organs leading to altered bioavailability, altered fluid status and inflammation resulting in altered distribution, and changes in drug metabolism due to the potential effect on liver microsomal enzymes and blood flow to the liver [62]. Additionally, renal excretion can change due to impaired renal function, requirement for dialysis, or augmented renal clearance [63]. Because pharmacokinetic studies are typically carried out in healthy volunteers, it can be difficult to extrapolate the information gathered from those studies to critically ill patients with many physiological changes. While there are retrospective studies that have demonstrated safety of lacosamide use in the ICU [64, 65], there is very limited evidence regarding potential pharmacokinetic changes of lacosamide in critically ill patients. A retrospective observational study of patients with refractory status epilepticus in the ICU described the efficacy of a weight-based IV loading dose of lacosamide [50]. The most efficacious loading dose in attaining a concentration in their suggested reference range of 15–20 mg/L was 10–12 mg/kg, although there was significant heterogeneity in plasma concentration based on loading dose. There are two limitations of this study, including the fact that the clearance and half life of lacosamide were not reported, making it difficult to determine if augmented renal clearance was occurring in the study population. Additionally, the relationship between

dose and efficacy was not stated, so we cannot be sure that attaining lacosamide concentration in the reference range correlated with efficacy of the medication. More evidence is needed in the critically ill population to elucidate pharmacokinetic changes of lacosamide.

4.9 Other

There are several other factors that may have an effect on the pharmacokinetics of lacosamide, including sex and presence of intellectual disabilities. Additionally, two case reports of lacosamide toxicity have been described.

The majority of studies did not find a difference in lacosamide plasma concentrations between sexes [5, 15, 28, 29, 48, 54]. Several of the studies at first found higher mean plasma concentrations of lacosamide in women; however, when the lower mean body weight of women was adjusted for, there was no significant difference.

One conference abstract of a retrospective observational study described comparable efficacy of lacosamide in people with and without intellectual disabilities [66]. While the authors did not report lacosamide serum concentrations to compare the two groups, they found that the serum concentration in both groups was 22 mmol/L. The concentration–dose ratio was similar between groups, at 0.07 in those with an intellectual disability and 0.06 in those without, so presumably the mean serum concentrations in each group was also similar. Likely, there are no major differences in the pharmacokinetics of lacosamide in people with intellectual disabilities compared with people without.

There have been three case reports associated with lacosamide toxicity. In a case report by Berei et al., a 70-year-old female experienced life-threatening ventricular tachycardia after administration of lacosamide 200 mg IV loading dose, then 300 mg IV every 12 h [67]. However, in this case study, lacosamide concentration at 2 days after starting lacosamide were within the suggested reference range at 12.4 mg/L. Using the Naranjo Probability Scale, the authors concluded that the relationship between lacosamide and ventricular tachycardia was ‘probable’. In another case report, a 26-year-old male experienced lacosamide toxicity after ingestion of 6,000 mg of lacosamide in a suicide attempt [68]. Lacosamide concentration at 10 h post-ingestion was well above the reference range at 44.5 mg/L. This overdose resulted in a paradoxical tonic–clonic seizure. Notably, there was no change in this patient’s renal function as a result of lacosamide toxicity. Another case report of lacosamide toxicity, including mental status changes and abnormal ECG, demonstrated the success of utilizing hemodialysis to clear lacosamide and bring the patient back to baseline [69].

4.10 Limitations

There are several limitations of this review. The majority of studies included are observational in nature, thus are subject to bias due to lack of randomization and blinding. Additionally, due to the relatively small sample size of many of the included studies there is the possibility that they were inadequately powered to detect significant differences. Another limitation is that many of the pharmacokinetic studies were conducted in healthy volunteers, which may not be entirely generalizable to a population with epilepsy.

4.11 Practical Aspects of Lacosamide TDM

If a clinician does choose to utilize TDM for lacosamide, there are several considerations. First, it is important to measure plasma concentrations at steady state, which is based on the half-life of the drug. It generally takes 3–5 half lives for a drug to reach a steady state. Based on its half-life of about 13 h in patients with normal renal and hepatic function, lacosamide is likely at steady state in 39–65 h (~2–3 days). With regard to sampling time, measuring a trough concentration (i.e., immediately before the next dose) is most consistent with the literature on TDM of lacosamide and will facilitate comparison of results overcoming concentration fluctuations [18]. Although it can be measured in some laboratories, lacosamide assay is not widely available. However, there are multiple methods that have been utilized in the literature, including LC–MS/MS [70, 71], GC–MS [72] and SPE–MS/MS [73]. Another consideration is the cost–benefit relationship of utilizing TDM; however, there is not currently any information on a cost–benefit relationship of lacosamide TDM. Further studies are needed.

5 Conclusion

Although TDM is not routinely performed to assess plasma concentrations of lacosamide, it may be a good way to ensure efficacy of seizure prevention and prevent toxicity and adverse reactions. If TDM is utilized, it is important to consider the plasma concentration together with the clinical context when making therapeutic decisions. While it may not be practical to utilize TDM for all patients, especially because lacosamide has predictable linear kinetics, there are some situations when TDM may be useful. The current literature shows that populations where TDM may be beneficial are in patients taking enzyme-inducer AEDs because of a potential drug interaction, in patients with decreased renal function or on dialysis and older adults. However, more evidence is needed in these situations, as well as in pediatrics, pregnancy, and in critical illness, to elaborate on potential pharmacokinetic variability of lacosamide due to

physiological changes that occur during these times. It is also imperative to establish a reference range for lacosamide that is accepted worldwide.

Acknowledgement Janice Kung, Librarian at John W. Scott Library, for assisting with the keywords selection and search strategy.

Author Contributions SHM had the idea of the article. LS performed the literature search and data abstraction and summarization. Both authors confirmed data collected and search and wrote the manuscript.

Compliance with Ethical Standards

Conflict of interest Authors have no conflicts of interest to declare.

Funding There is no funding associated with this work.

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