Seizure 25 (2015) 1–17

Contents lists available at ScienceDirect

Seizure

journal homepage: www.elsevier.com/locate/yseiz

Review

# Lacosamide as adjunctive therapy in refractory epilepsy in adults: A systematic review

Vanessa Paquette [a], Celia Culley [b], Erica D. Greanya [c,d], Mary H.H. Ensom [a,d,*]

[a] Department of Pharmacy, Children's and Women's Health Center of British Columbia, 4480 Oak Street, Vancouver, British Columbia, Canada V6H 3V4
[b] Department of Pharmacy, Royal Jubilee Hospital, 1352 Bay Street, Victoria, British Columbia, Canada V8R 1J8
[c] Department of Pharmacy, Victoria General Hospital, 1 Hospital Way, Victoria, British Columbia, Canada V8Z 6R5
[d] Faculty of Pharmaceutical Sciences, The University of British Columbia, 2405 Wesbrook Mall, Vancouver, British Columbia, Canada V6T 1Z3

ARTICLE INFO

*Article history:*
Received 30 September 2014
Received in revised form 14 November 2014
Accepted 18 November 2014

*Keywords:*
Antiepileptic drug
Anticonvulsant
Seizure
Status epilepticus

ABSTRACT

*Purpose:* To review the evidence for efficacy and safety of lacosamide in adult patients with refractory epilepsy and refractory status epilepticus (RSE).
*Methods:* A systematic literature search of MEDLINE, PubMed, EMBASE, IPA, Google and Google Scholar (through October 2014) was performed.
*Results:* Fourteen studies assessing lacosamide in 3509 refractory epilepsy patients were included. In 3 RCTs, more patients had at least 50% reduction in seizure frequency with lacosamide compared to placebo with 38.3–41.1%, 38.1–41.2%, and 18.3–25.8%, in the 400 mg/day, 600 mg/day, and placebo groups, respectively. In non-comparative trials, 18–69% of patients achieved at least 50% reduction in seizure frequency, and 1.7–26.2% achieved seizure freedom. Non-responders were documented in two trials, with 26.2–34% having no response. Thirteen studies assessing lacosamide in 390 RSE patients were included. When assessing lacosamide's ability to terminate RSE, one comparative cohort study found no improvement in SE duration or seizure control with addition of lacosamide. Another study documented no difference compared to use of phenytoin. Eleven descriptive studies using lacosamide as add-on RSE therapy revealed seizure termination rates of 0–100% (median 64.7%). In all patients receiving lacosamide, dizziness (21.8%), vision disturbances (10.4%), drowsiness (7.4%), headache (7.0%), nausea (6.5%), and coordination problems (5.8%) were the most common adverse effects.
*Conclusion:* Based on evidence to date, adjunctive lacosamide is a treatment option to reduce seizure frequency in patients with refractory epilepsy and terminate seizures in patients with RSE. The safety information summary can be used to advise patients of potential adverse effects.


## 1. Introduction

Epilepsy affects up to 2% of the worldwide population, making it one of the most common neurological disorders.[1] Despite the availability of numerous antiepileptic drugs (AEDs) and the continuing emergence of novel AEDs, 30% of patients with epilepsy still suffer from uncontrolled seizures and many experience unpleasant adverse effects.[2]

Refractory epilepsy is defined by the International League Against Epilepsy (ILAE) as failure of adequate trials of two tolerated and appropriately chosen and used AED schedules, whether as monotherapies or in combination, to achieve sustained seizure freedom.[3] Currently, some available therapeutic options to help control refractory epilepsy include adjunctive sodium-channel blockers (carbamazepine, lamotrigine, phenytoin, oxcarbazepine), gamma-aminobutyric acid (GABA) inhibitory transmission potentiators (valproic acid, topiramate, clobazam, vigabatrin, phenobarbital), calcium channel modulators/inhibitors (gabapentin, pregabalin, zonisamide, ethosuximide) and synaptic vesicle protein 2A stimulators (levetiracetam), depending on the epilepsy syndrome and seizure type.[4] Similarly, refractory status epilepticus (RSE) is defined as failure of first and second-line agents to terminate the seizure, requiring the addition of a third agent.[5] Many of the same therapeutic options,

* Corresponding author at: Department of Pharmacy, Children's and Women's Health Center of British Columbia, 4480 Oak Street, Vancouver, British Columbia, Canada V6H 3V4. Tel.: +1 6048752886.
*E-mail addresses:* vpaquette@cw.bc.ca (V. Paquette), celia.culley@viha.ca (C. Culley), erica.otto@viha.ca (E.D. Greanya), ensom@mail.ubc.ca (Mary H.H. Ensom).

http://dx.doi.org/10.1016/j.seizure.2014.11.007
1059-1311/

especially those available in intravenous form, are being investigated in the treatment of RSE.[6]

Lacosamide is a new AED believed to exert its anticonvulsant effects through two novel mechanisms of action. The first is through its enhancement of slow inactivation of voltage gated sodium channels (VGSC). Depolarization of VGSCs allows sodium ion influx across neuronal cell membranes, an important step in the initiation of the action potential. After depolarization, VGSCs enter an inactivated state before reverting back to their resting state (where they are available for depolarization again). During the inactivated state, VGSCs are unavailable for depolarization. This fast, inactivated state is milliseconds long and is the site of action of the traditional sodium-channel blockers. In conditions of sustained depolarization and repetitive firing such as epilepsy, VGSCs can undergo a conformational change into the slow inactivation state, which is seconds long. Lacosamide enhances this transition of VGSCs into the slow inactivated state, reducing the availability of VGSCs for depolarization and subsequent neuronal firing.[7]

The second potential mechanism of action is lacosamide's binding to collapsin response mediator protein 2 (CRMP-2), which is involved in neuronal differentiation, polarization, and axonal outgrowth.[1] To date, the exact effects of the interaction of lacosamide and CRMP-2 on seizure control have not been determined, and one study suggests lacosamide does not, in fact, bind to CRMP-2.[8]

Lacosamide is available as intravenous (IV) and oral formulations. Lacosamide has 100% bioavailability after oral administration and exhibits linear (dose-proportional) pharmacokinetics. Lacosamide's volume of distribution is approximately 0.6 L/kg and binding to plasma proteins is <15%. Lacosamide is metabolized by CYP2C19, CYP2C9, and CYP3A4 into the pharmacologically inactive O-desmethyl-lasosamide. Ninety-five percent of the lacosamide dose is excreted in urine; of this, 40% as unchanged drug, 30% as O-desmethyl-lacosamide, and the remainder as small amounts of additional metabolites. Lacosamide has an elimination half-life of approximately 13 h and appears to have no appreciable pharmacokinetic drug interactions.[9]

Advantages of lacosamide as an AED include its availability as both oral and IV formulations, excellent bioavailability, minimal drug interactions, and novel mechanisms of action.

Lacosamide has been available in Europe and the USA since 2008 and in Canada since 2010.[9] The purpose of this paper is to systematically review the available evidence for the efficacy and safety of lacosamide in adult patients with refractory epilepsy and RSE.

## 2. Methods

A search of MEDLINE (1948–October 2014), PubMed (1946–October 2014), EMBASE (1980–October 2014), IPA (1970–October 2014), Google and Google Scholar was conducted for articles describing the efficacy and safety of lacosamide in adult patients with refractory epilepsy or RSE. The following search terms were used: lacosamide or harkoseride or Vimpat and epilepsy or seizure or status epilepticus. Reference lists of all identified articles were manually searched. Studies were included if patients were >16 years of age and treated with lacosamide for refractory epilepsy or RSE.

The recent definition of refractory epilepsy (provided by the ILAE) and that of RSE suggest patients should have failed at least two AEDs. In order to ensure all applicable studies were adequately captured, on initial review we included studies that defined refractory epilepsy conservatively as failure to respond to one or more AEDs, provided the population median of failed AEDs prior to lacosamide introduction was 3 or greater. Studies with the following characteristics were excluded: non-human data, not published in English, and published as single case reports or abstract only.

Each study was ranked on the basis of quality of evidence it provided according to the US Preventive Services Task Force 1996 classification system.[10] Level I studies are randomized controlled trials. Level II-1 articles are controlled studies, with patients acting as their own controls or with a parallel control group included. Level II-2 articles are defined as cohort or case–control studies. Level II-3 articles are multiple time series or exceptional descriptive studies. Level III studies are defined as descriptive studies and case reports.[10]

Information extracted included study design, number of participants, characteristics of the study population, including previously tried antiepileptic drugs when available, lacosamide dosing regimens, outcome measures, adverse events and any information available on therapeutic drug monitoring.

## 3. Results

For refractory epilepsy, the search produced 20 studies, 14 of which were included in this review. Three studies were classified as level I evidence and the remaining 11 were classified as level III evidence. Of the 6 excluded studies, one study was conducted solely in critically ill patients and was included in the RSE review, one study included patients only with brain tumor-related epilepsy, one study did not look at any efficacy outcomes, and 3 studies were single case reports. Results of each study included are described below and summarized in Table 1.[11–24] For RSE, the search produced 22 studies, 13 of which were included in this review. No level I evidence was available. Two studies were level II-2 and the remaining 11 were classified as level III evidence. All 9 excluded studies were single case reports. Results of each study included are described below and summarized in Table 2.[25–37]

### 3.1. Efficacy of lacosamide in refractory epilepsy

#### 3.1.1. Level I evidence

Three randomized controlled trials (RCTs) have been conducted assessing the efficacy and safety of lacosamide as adjunctive treatment in adults with refractory epilepsy. All three trials include patients with only focal seizures.[11–13]

In the first RCT by Ben-Menachem et al.,[11] patients were randomized to receive oral lacosamide 200 mg/day (100 mg BID), 400 mg/day (200 mg BID), 600 mg/day (300 mg BID) (see Table 1 for titration protocol) or placebo. Patients were eligible if they had focal seizures for at least 2 years despite previous therapy with at least 2 other AEDs and had at least 4 seizures per month (with no seizure-free period longer than 21 days) during an 8-week baseline phase. If patients experienced adverse events during the titration phase, dose reduction was allowed once before the patient was discontinued from the trial. Patients then entered a 12-week maintenance phase.[11]

Of the 421 patients randomized, 6 were not included in the efficacy analysis due to protocol non-compliance and no post-baseline efficacy assessments.[11]

The intention-to-treat (ITT) populations for lacosamide 400 mg/day and 600 mg/day demonstrated statistically significant median percent reductions in seizure frequency (compared to the placebo group) and proportion of patients with at least 50% and 75% reductions in seizure frequency (Table 1). Seven patients experienced seizure freedom for the entire 12-week maintenance period (1 in 200 mg/day, 5 in 400 mg/day, and 1 in 600 mg/day groups). Median change in percentage of seizure-free days (i.e., 12%) was statistically significant in both 400 mg/day and 600 mg/day groups.[11]