Adjunctive lacosamide in clinical practice: Sodium blockade with a difference?

AUTHORS: Linda J Stephen, Kevin Kelly, Pamela Parker, Martin J Brodie
JOURNAL: Epilepsy & Behavior

Keypoints

- This article reports the preliminary outcomes of the first prospective study of lacosamide as adjunctive therapy in the clinical setting – the findings are particularly relevant to daily clinical practice as such pragmatic/observational studies provide useful/complementary information to that obtained from regulatory trials.

- The analysis was conducted on data from 65 of 113 (57.5%) enrolled patients who reached an endpoint.

- Seventeen (26.2%) patients remained seizure free for ≥6 months on a median lacosamide daily dose of 100 mg (range 50–300 mg).

- Seizure freedom was more likely when lacosamide was used as a first add-on compared with a later treatment schedule (41.7% vs. 3.7%, p=0.001).

- Lacosamide was withdrawn in 14 patients (among a total of 113); 10 for side effects and 4 for lack of efficacy. Withdrawal due to side effects was greatest among patients taking the combination of lacosamide and sodium valproate.

- In patients with partial-onset seizures, lacosamide is an effective and well-tolerated adjunctive anti-epileptic drug when combined with appropriate doses of traditional sodium blocking anti-epileptic drugs, as well as those with other mechanisms of action.

Background and objectives

- The efficacy and safety of lacosamide in the treatment of adult patients with partial onset seizures was established in three pivotal Phase II/III trials (SP667, SP754 and SP755).1–3
- Double-blind, randomized controlled trials (RCTs) are the cornerstone of evidence-based medicine; however, they have several important limitations. Notably, in RCTs for antiepileptic drugs (AEDs), the inclusion criteria, dosing and titration schedules are very strict. Therefore, RCTs do not fully reflect clinical practice, and data from RCTs have limited clinical applicability to the routine, everyday use of the drug outside of the RCT.
- In the 'real-life' setting of routine clinical practice, patients constitute an extremely heterogeneous population; therefore, observational clinical studies are important in providing clinical data about the use of a drug that can complement those obtained from pivotal, registration trials.
- This observational study was conducted to examine the everyday use and determine the pros and cons of adjunctive lacosamide in routine clinical practice in patients with partial onset seizures.
**Study design and outcomes**

- Prospective observational study with:
  1. Seizure freedom for ≥6 months on a given lacosamide dose (target range 200–400 mg/day)
  2. ≥50% reduction in seizures (responder) for ≥6 months on the highest tolerated lacosamide dose
  3. <50% reduction in seizures (marginal response) for ≥6 months on the highest tolerated lacosamide dose
  4. Lacosamide withdrawal because of side effects, lack of efficacy, or both

**Methods**

- Patients were on a stable AED regimen for 3 months when lacosamide was added

  - The starting dose was 50 mg daily for 2 weeks, increasing to 50 mg twice daily thereafter, with a target dose of 200–400 mg/day

- Titration continued until one of the aforementioned endpoints was reached

**Results**

- A total of 113 patients with uncontrolled focal seizures were treated with adjunctive LCM, and of these, 65 (57.5%) reached a study endpoint – data from these patients were included in the analyses

  - In total, 17 (26.2%) patients became seizure free on a stable lacosamide dose (median dose 100 mg/day, range 50–300 mg) for a 6-month period
  - Two patients were established on LCM monotherapy following withdrawal of their original AED (please note lacosamide monotherapy is off-label)
  - Patients were more likely to remain seizure free when lacosamide was used as first add-on compared with a later treatment schedule (41.7% vs. 3.7%, p=0.001) (see Figure 1)

The following patient grouping were identified based on AED combinations

<table>
<thead>
<tr>
<th>Patient group</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lacosamide + traditional SCB only</td>
<td>8 (12.3%)</td>
</tr>
<tr>
<td></td>
<td>Carbamazepine, phenytoin, lamotrigine, oxcarbazepine</td>
</tr>
<tr>
<td>Lacosamide + AED with other MoA only</td>
<td>37 (56.9%)</td>
</tr>
<tr>
<td></td>
<td>Topiramate, levetiracetam, zonisamide, pregabalin, valproate, phenobarbital</td>
</tr>
<tr>
<td>Lacosamide + traditional SCB + AED with other MoA</td>
<td>18 (27.7%)</td>
</tr>
</tbody>
</table>

SCB = sodium-channel blocker; MoA = mechanism of action
**Figure 1.** Percentage of patients who became seizure free when given adjunctive lacosamide.

- Efficacy analyses based on the sodium channel blocking properties of concomitant AEDs, indicated that seizure freedom rate was numerically greater among patients taking concomitant AEDs with other MoA compared with those taking traditional SCBs (29.7% vs. 19.2%); however, a statistical analysis was not performed.

**Figure 2.** Percentage of patients who became seizure free when adjunctive lacosamide was combined with a sodium channel blocking agent or a non-sodium channel blocking agent.

- Lacosamide retention rates were similar among patients taking traditional SCBs (22/24, 84.6%) and those taking AEDs with other MoA only (27/37, 72.9%)
- Lacosamide was withdrawn in 14 patients so far in the entire study population (N=113), 10 due to side effects and 4 due to lack of efficacy
- Side effects leading to withdrawal included sedation, ataxia, dizziness, agitation, tremor, headache, diplopia, dysarthria, nausea and vomiting
- Patients taking lacosamide and concomitant valproate were more likely to discontinue than those taking other AEDs (8/21, p=0.018)
**Discussion**

- Overall, in this study, 6-month seizure freedom was documented in 26.2% of patients taking a median daily lacosamide dose of 100 mg.

- Outcomes, including seizure freedom, were similar among patients taking traditional SCBs and those taking AEDs with other MoA only.

- While this finding does not fully corroborate the findings of the Saké *et al.* post hoc analysis, it is essential to note that this current study was an observational study based on real life clinical practice, and therefore had a number of important differences with the pivotal trials of lacosamide. Notably, in the pivotal trials:
  - Patients were more likely to suffer from difficult-to-control seizures – before addition of lacosamide, they had a median of 11–13, 11.5–16.5, and 9.9–16.5 seizures per 28 days, depending on the trial, compared with a median frequency of 4 per month for patients in this audit.
  - The majority of patients had seizures that were not controlled by at least 2 AEDs, whereas more than 50% in this audit were taking 1 AED only when lacosamide was added.
  - Doses of 200, 400, or 600 mg/day with fixed titration schedules were used, whereas dosing was completely flexible in this audit (please note lacosamide monotherapy is off-label).

- This audit also showed that if lacosamide was used as first add-on rather than a later treatment schedule, the likelihood of seizure freedom would be significantly higher.

- Patients taking concomitant valproate were more likely to discontinue lacosamide than those taking other concomitant AEDs. This may be explained by the observation that VPA also acts at voltage-dependent sodium channels.

**Conclusions**

- Lacosamide was found to be an effective and well-tolerated adjunctive AED when used to treat patients with uncontrolled partial-onset seizures in everyday clinical practice – overall, 78% of patients benefited from the addition of LCM to their AED regimen.

- Seizure freedom rates was more likely as a first add-on than as a later treatment schedule.

- Seizure freedom and retention rates were similar among patients taking concomitant traditional SCBs, and those taking concomitant AEDs with other MoA.
These preliminary results are the first prospective, pragmatic data that support and complement the evidence on the efficacy and tolerability of adjunctive lacosamide obtained from the pivotal trials.

Results of this article can be used as evidence to support the use of lacosamide in any AED combination, regardless of the MoA of the concomitant AED(s).

The study provides useful insight on the use of lacosamide in the daily practice of clinicians and supports the efficacy and safety of lacosamide as first/early add-on for patients with uncontrolled partial-onset seizures.

Please note that neither the 600 mg dose of lacosamide, nor its use as monotherapy are approved; therefore these elements should not be promoted.

References


Contains off-label information. For internal use and educational purposes only. Do not circulate outside. Unsolicited request about off-label information should be addressed to medical staff only. VIMPAT® is indicated as adjunctive therapy in the treatment of partial onset seizures with or without secondary generalisation in patients with epilepsy aged 16 years and older in Europe. Please consult the locally approved prescribing information.