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Review Article

# Role of Lacosamide in Seizure Control in Brain Tumor Patients

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**Abstract**

Lacosamide is a new antiepileptic drug that was has been approved as an adjunctive treatment of partial-onset seizures but also has potential in brain tumor-related epilepsy. The medication's novel mechanism of action of selectively enhances slow inactivation of sodium channels and does not affect the rate of recovery. Lacosamide is available in both oral and intravenous preparation for ease of use and have has 100% bioavailability. Lacosamide is not metabolized by nor induces the activity of cytochrome P450. There is no significant interactions with other antiepileptic or chemotherapy drugs. Seizure control rate is very good with 50% respond rate range between 54-78%. The side effects of lacosamide are usually well tolerated, most commonly and include dizziness, blurry vision, nausea and vomiting. Although there are only a small number of retrospective studies of lacosamide in brain tumor patients with seizure, the results are promising. Lacosamide is an excellence choice as an add-on agent for brain-tumor patients with epilepsy resistant to one or more first line AEDs.

## INTRODUCTION

Brain tumor-related epilepsy is challenging to treat. Thirty to fifty percent of patients with brain tumors will present with seizures and 10-30% of these patients can have recurrent seizures [1,2]. It can be difficult to control recurrent seizures especially when first-line drugs like levetiracetam are ineffective.

### Role of lacosamide in partial onset seizures

Lacosamide (LCM) is a new Antiepileptic Drug (AED) that was approved by the Federal Drug Administration for adjunctive treatment of partial-onset seizures in patients 17 years or older [3]. Lacosamide has a novel and unique mechanism of action at the voltage-gated sodium channels by selectively enhances enhancing slow inactivation of the channel and reduces the voltage-gated sodium channels availability. In contrast to carbamazepine, lamotrigine, and phenytoin, lacosamide's action does not affect the fast inactivation of the voltage-gated sodium channels and does not alter the rate of recovery [4,5]. The selectivity of lacosamide allows for therapeutic action against pathophysiological hyperactivity, but does not affect physiological activity of the channel [4,6,7]. LCM also has a second mechanism of binding to the collapsin response mediator protein-2 (CRMP-2) and modulates mCRMP2 function. The binding appears to reduce the axonal outgrowth in respond response to neurotrophic factors [6,8].

LCM, like Levetiracetam (LEV), is available in both oral and intravenous form. The usual oral dose is 200-600 mg divided into twice-daily doses. Also like levetiracetam, intravenous admission has the same bioavailability as the oral form. When convert to the intravenous form, the same dose of lacosamide can be infuse infused over thirty to sixty minutes [9]. Lacosamide has a half-life of thirteen hours [10], which allows for convenient twice daily dosing. Lacosamide is not metabolized by nor induces the activity of cytochrome P450 [11] and has no significant effects on plasma concentrations of other AEDs (including gabapentin, topiramate, lamotrigine, carbamazepine, levetiracetam, phenytoin, phenobarbital, oxcarbazepine, valproic acid) [12]. Enzyme-inducing antiepileptic medications, however, can decrease the level of LCM in the blood by 15 to 20% [6]. Levetiracetam exhibits similar characteristics, having low potential for interactions with other AEDs or chemotherapy drugs [13,14]. These characteristics make LCM and LEV stand out among AEDs. Older generation AEDs are notorious for interaction with other drugs, including other AEDs, chemotherapy drugs, and medications metabolized by cytochrome P450 (Table 1).

LCM and LEV both have no significant interactions with typical chemotherapies used for brain tumors. In contrast, enzyme-inducing AEDs like phenobarbital, carbamazepine, phenytoin, and primidone are known to accelerate metabolism of chemotherapeutics and decrease the effective chemotherapy agents' level in the blood [15,16]. The enzyme-inducing AEDs

**Table 1:** Can you provide a title?

| | Lacosamide | Levetiracetam |
|---|---|---|
| MOA | -Selectively enhances slow inactivation of sodium channels<br>-Binds to CRMP2 and mCRMP2 [7] | -Bind inhibits presynaptic vesicle exocytosis and decrease neurotransmitter release. [37] |
| FDA approved use | Adjunctive treatment for partial-onset seizures, with or without secondary generalization, in patient 17 years or older [3]. | Myoclonic, partial onset, and tonic-clonic seizures |
| Available preparations | IV and PO | IV and PO |
| Usual Dose | Initial 50 mg twice a day, may increased 100mg daily/week<br>Maintenance dose 200-600 mg daily | Initial 500 mg twice a day, may increase every 2 weeks by 500 mg/dose.<br>Maintenance dose 1000-3000 mg daily |
| Bioavailability | Same bioavailability PO or IV [9] | 100% [13] |
| Half life | 13 hrs [10,35] | 6-8 hours<br>Extended tab 7 hours |
| Cyt P450 metabolism | Not metabolized by or induce activity of cyt P450 [11] | Not metabolized by or induce activity of cyt P450 [17] |
| Elimination | 40% eliminated in urine unchanged<br><30% as O-desmethyl metabolite. [11]<br>Renal dosing: if Clcr < 30ml/min/1.73m2. Maximum 300 mg daily<br>Hepatic dosing: mild to moderate impairment. Maximum 300 mg daily | 66% eliminated in urine unchanged.<br>Renal dosing required.<br>Hepatic dosing: severe impairment, decrease dose by 50% in patient who also have Clcr < 60mL/min/1.73m2 |
| Interaction with other AED | -LCM had no relevant influence on plasma concentrations of concomitant AEDs (including gabapentin, topiramate, lamotrigine, carbamazepine, levetiracetam, phenytoin, phenobarbital, oxcarbazepine, valproic acid) [12]<br>-blood level of LCM is decreased by approximately 15–20% by enzyme-inducing antiepileptic medications [6] | Low potential for interactions with other antiepileptic [14,24]. |
| Interaction with chemotherapy | Does not significantly interact with chemotherapy drugs.<br>May protect again alkylating agent chemotherapy induced painful neuropathy [20]. | Does not significantly interact with chemotherapy drugs [14,24].<br>Increase sensitivity of Glioblastoma tumors to temozolomide [21-24]<br>Free-radical scavenging, neuroprotective effect [26]. |
| Seizure reduction (50% respond rate) | Monotherapy for partial seizure [6,9]<br>200 mg 34%<br>400 mg 40%<br>Placebo 23%<br>Add-on or Monotherapy for BTRE [32]<br>54%<br>Add-on therapy for BTRE [11]<br>78% | BTRE<br>>60% [38]<br>91% seizure free with monotherapy [39i] |
| Side effects | Most common dizziness, nausea, vomiting, ataxia, vision abnormal, diplopia, and nystagmus [12,36] | HTN, behavior problems, vomiting, weakness, nasopharyngitis |
| Role in BTRE | Excellence choice as an add-on agent for BT patient with epilepsy resistant to one or more first line AEDs<br>LCM has not been studied as a monotherapy for BTRE | Excellence choice as a first line agent or add-on for BTRE. |

have been shown to reduce the effectiveness of taxanes, vinca alkaloids, methotrexate, teniposide, and camptothecin analogues such as irinotecan [17-19]. Additionally, LCM may protect against alkylating chemotherapy induced painful neuropathy [20]. A study in rats demonstrated that those treated with lacosamide did not develop vincristine-induced cold allodynia [20]. Levetiracetam also has favorable side effects. The first involves increase sensitivity of Glioblastoma tumor to temozolomide by suppressing the expression of temozolomide inhibitor Methylguanine-DNA-methyltransferase (MGMT) [21-24]. LEV also has free-radical scavenging action that is neuroprotective [25,26].

The efficacy and safety of lacosamide has been studied closely previously in non-brain tumor patients with partial seizures. Halford et al reviewed three randomized trials of lacosamide use in partial seizures, one phase II study (SP667) [27] and two phase III studies (SP754 and SP755) [6,28,29]. Each of the studies included 400 to 500 subjects with uncontrolled partial-onset seizures. The inclusion criteria included having at least four partial-onset seizures in a 28-day period, within eight-week baseline phase, and no seizure-free period longer than 21 days. LCM was studied as an add-on therapy to other AEDs with or without a vagus nerve stimulator. These studies showed that at a dose of 400 mg/day, there is a statistically significant improvement of 50% in the responder rate (39% compared to placebo of 21%) and median percentage seizure reduction (37% compared to placebo of 17%). The absolute median reduction in seizure frequency over placebo at this dose is 20%. SP667 and SP754 showed that 600 mg/day dosing did not significantly improve outcomes compare to 400 mg/day. A 400 mg daily

dose displays best risk/benefit ratio. A daily dose of 200 mg was not consistently better than placebo and 600 mg daily dose had more CNS side effects and expense. Most of the side effects were dose-dependent and related to the CNS, included dizziness, nausea, diplopia, ataxia, abnormal coordination, vomiting and nystagmus. There were no reports of rash, hyponatremia, cognitive slowing, or change in hematology, blood chemistry, and vital signs [12,29,30].

### Role of lacosamide in brain tumor-related epilepsy

Fonkem et al previously reviewed two studies involving the use of lacosamide in brain tumor-related epilepsy, a retrospective chart review by Saria et al and a cases series by Maschio et al [11,31,32]. The retrospective chart review was done conducted at five medical centers in the United States which included seventy patients with primary brain tumors including 96% had gliomas (glioblastoma (40%), grade II gliomas (36%), grade III anaplastic astrocytomas, anaplastic/atypical meningiomas, anaplastic ependymomas, and pleomorphic xanthoastrocytomas). Fifty-five patients (78%) had partial seizures and twelve patients (17%) had generalized seizures. Lacosamide was chosen in the majority of the patients (74%) because of recurrent seizure. Fifty-nine patients (84%) had chemotherapy, fifty-seven patients (81%) had radiation, and forty-four patients (63%) had surgical treatment with craniotomy. Fifty-eight patients (83%) were taking other AEDs concurrently with lacosamide, most commonly leveteracetam levetiracetam.

Seizure frequency was reduced in forty-six patients (66%) and unchanged in twenty-one patients (30%). Thirty-eight patients (54%) were seizure free or had seizure frequency reduced by at least 50%. Fifty-four patients (77%) reported no toxicities. Most common toxicities were fatigue, dizziness, confusion, weakness, and nausea. The authors concluded that lacosamide was well tolerated and effective in patients with brain tumors [32].

One case series by Maschio et al reported fourteen patients with brain tumor-related epilepsy who were started on lacosamide as an add-on to other AEDs [11]. These patients had at least one seizure per month on combination of one or more of leveteracetam levetiracetam, valproic acid, lamotrigine, phenytoin, zonisamide, and oxcarbazepine. Lacosamide was started at 100 mg/day and increased to effect by 100 mg/day or to a maximum of 400 mg/day (Table 1). The follow up periods ranged from less than 1 month to 10 months with nine patients passing away during the periods. The average follow up period was 5.4 months. Eleven patients underwent chemotherapy while being treated with LCM. The number of mean seizures was decreased from 15.4 to 1.9 per month after addition of LCM. This was statistically significant with a P-value = 0.022. The average lacosamide dose was 332.1 mg/day. Six patients (42.9%) were seizure free and five patients (36%) had reduction in seizure frequency by at least half. Fifty percent respond rate was 78.6%. One patient had no change in seizure frequency. The medication was well tolerated. Only one patient discontinued LCM because of blurry vision and dizziness. The authors concluded that lacosamide is an effective add-on AED in patients with BTRE [11].

Newton et al did performed a retrospective review of lacosamide effectiveness in thirteen patients with seizure disorder and brain tumor [33]. Lacosamide was used as an add-on therapy in eleven patients and as monotherapy in two patients. There were eight males men and five females women with an average age of 47 (ranges 31-70). The primary brain tumor types included median age of 47 years (range 31-70). The types of PBT included GBM – 4, oligo – 4, oligoastrocytoma – 1, pilocytic astrocytoma – 1, pineoblastoma – 1, DNET – 1, and gliomatosis cerebri – 1. Lacosamide was used as monotherapy in two patients and add-on in eleven patients. The median dose was 100 mg/day (range 50-225 mg/day). Six patients (46%) had complete control of seizure. The seizure frequency was reduced in 10 patients (77%) and the median seizure frequency was decreased from once every 2 weeks to less than once a month. The most common side effect was mild dizziness [33].

Sierra-Marcos and associates reviewed five case studies where lacosamide was used in epileptic patients with comorbidities and unusual presentations [34]. The first patient was a 52-year-old man with progressive difficulties understanding verbal language and receptive dysphasia. The patient also complained of ascending paresthesia and feeling of coldness in the upper right extremity lasting 30 seconds, not associated with involuntary movements. MRI showed hyperintensity at the left insular level. EEG showed irritative focus at the left temporal level. The patient had a left parahilar adenopathy that was biopsied and turned out to be microcytic lung carcinoma. He had paraneoplastic encephalitis due to the lung cancer. Valproic acid 500 mg every 8 hours and lacosamide 200 mg every 12 hours were started along with chemotherapy and radiation therapy. The patient was admitted for the language and neurological deficits. Intravenous benzodiazepine was used and the patient continued on same dose of valproic acid. However, EEG showed persistent pathologic waveforms after four days. Lacosamide was restarted at 50 mg/12 hours and increased to 400 mg/day by increment of 100 mg/week. Repeat EEG showed disappearance of epileptiform in left temporal area. In a second case, a 47-year-old patient with astrocytoma had complex partial and secondary generalized seizures after surgical resection of the tumor. The seizures were not controlled with phenytoin 150 mg/12 hours or levetiracetam 3000 mg/day. Six months after surgery, the patient continue to have seizures about every two weeks. Lacosamide was added to levetiracetam. This reduced the seizure frequency to one every 2 months. The last three patients had Alzheimer's disease, catamenial epilepsy, and refractory convulsive status epilepticus. All three patients have had seizures that improved after lacosamide was added [34].

## CONCLUSION

Lacosamide is a new AED that has novel and unique mechanisms of actions. The medication is available in both intravenous and oral preparation with 100% bioavailability. There is limited drug interaction between other AEDs or chemotherapy drugs. Lacosamide does not induce or affected by activity of cytochrome P450. The small numbers of retrospective studies of lacosamide in brain tumor patients with seizure showed that seizure control rate is very good with 50% respond rate range between 54-78%. Side effects of lacosamide are minimal and usually well tolerated. These side effects most commonly include dizziness, blurry vision, nausea and vomiting. All these

characteristics make lacosamide an excellence choice as an add-on agent for brain-tumor patients with epilepsy resistant to one or more first line AEDs. LCM has not been studied extensively as a monotherapy for BTRE brain tumor-related epilepsy. Future studies should investigate further the role of LCM as a monotherapy for BTRE brain tumor-related epilepsy.

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