Epilepsy Currents
2021, Vol. 21(5) 326–328

DOI: 10.1177/15357597211025132
journals.sagepub.com/home/epi
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A "Sodium Drug" for Generalized Epilepsy? A Mystery That Still Needs to be Solved

Comment on: Vossler DG, Knake S, O'Brien TJ, et al. Efficacy and safety of adjunctive lacosamide in the treatment of primary generalised tonic-clonic seizures: a double-blind, randomised, placebo-controlled trial. *J Neurol Neurosurg Psychiatry*. 2020;91(10):1067-1075. doi:10.1136/jnnp-2020-323524

Objective: To evaluate efficacy and safety of lacosamide (up to 12 mg/kg/day or 400 mg/day) as adjunctive treatment for uncontrolled primary generalised tonic-clonic seizures (PGTCS) in patients (≥4 years) with idiopathic generalised epilepsy (IGE). Methods: Phase 3, double-blind, randomised, placebo-controlled trial (SP0982; NCT02408523) in patients with IGE and PGTCS taking 1-3 concomitant antiepileptic drugs. Primary outcome was time to second PGTCS during 24-week treatment. Results: 242 patients were randomised and received ≥ 1 dose of trial medication (lacosamide/placebo: n = 121/n = 121). Patients (mean age: 27.7 years; 58.7% female) had a history of generalised-onset seizures (tonic-clonic 99.6%; myoclonic 38.8%; absence 37.2%). Median treatment duration with lacosamide/placebo was 143/65 days. Risk of developing a second PGTCS during 24-week treatment was significantly lower with lacosamide than placebo (Kaplan-Meier survival estimates 55.27%/33.37%; HR .540, 95% CI 0.377 to .774; $P < .001$; n = 118/n = 121). Median time to second PGTCS could not be estimated for lacosamide (>50% of patients did not experience a second PGTCS) and was 77.0 days for placebo. Kaplan-Meier estimated freedom from PGTCS at end of the 24-week treatment period (day 166) for lacosamide/placebo was 31.3%/17.2% (difference 14.1%; $P = .011$). More patients on lacosamide than placebo had ≥ 50% (68.1%/46.3%) or ≥ 75% (57.1%/36.4%) reduction from baseline in PGTCS frequency/28 days, or observed freedom from PGTCS during treatment (27.5%/13.2%) (n = 119/n = 121). 96/121 (79.3%) patients on lacosamide had treatment-emergent adverse events (placebo 79/121 (65.3%)), most commonly dizziness (23.1%), somnolence (16.5%), headache (14.0%). No patients died during the trial. Conclusions: Lacosamide was efficacious and generally safe as adjunctive treatment for uncontrolled PGTCS in patients with IGE.

In 2001 and again in 2005, Karceski and colleagues provided an expert opinion for the treatment of epilepsy in adults.[2,3] This expert opinion was sought after in response to the glaring deficiencies in the literature available at that time regarding comparisons between the efficacy of specific treatments, lack of data regarding combination therapies, or randomized controlled trials assessing efficacy of anti-seizure drugs (ASDs). One of the focus areas were idiopathic generalized seizures and epilepsies (IGEs) with specific division between generalized, absence and myoclonic seizures and between first/initial and subsequent therapies. In general, at that time valproate, lamotrigine, topiramate, and zonisamide were considered the best initial and second line therapies for primary generalized tonic-clonic seizures (PGTCS) with addition to the mix of ethosuximide and clonazepam in case of absence and myoclonic seizures. As it frequently goes with an expert opinion, it gets modified and changed when new data become available and so was the case here. The main change in the 2005 expert consensus was the addition of levetiracetam and clobazam to the mix.[3] Despite these additions, choices were not abundant and some medications were "blacklisted". Fortunately, since then, many new ASDs became available and trials of the newly available and "old" medications have been conducted in patients with IGEs to answer the questions regarding medication choices – these include not only several randomized, double-blind, placebo-controlled trials assessing efficacy of specific drugs (eg, topiramate, lamotrigine, levetiracetam, brivaracetam, or perampanel) but also comparative trials of several ASDs including the SANAD trials.[4,5] Further, the focus of some of the trials has not been on PGTCS but, in some cases, on other generalized seizure types – absences and myoclonic seizures.[6,7] The randomized, double-blind, placebo-controlled trial of lacosamide (LCM) in children and adults with PGTCS discussed here adds to the existing evidence.[1]

Before we discuss the new data, we need to better understand why LCM, a "sodium drug", would work for the treatment of PGTCS. If we consider the other "sodium drugs" eg, carbamazepine or phenytoin, their efficacy for controlling seizures in generalized epilepsies is low and they are frequently reported to worsen generalized epilepsies[8] – in fact, the expert opinion clearly placed these ASDs towards the bottom third of potential treatment selections in all categories – PGTCS, absence, and myoclonic seizures.[2,3] While many of us have been using LCM for the treatment of seizures in patients with IGEs since it became available, I doubt any of us know what makes the

mechanism of action of LCM so special that this drug is worth studying for the treatment of PGTCS (and that it actually works in PGTCS). The answer to this question is unfortunately not very clear as the mechanism of action of LCM has not been fully elucidated to date.[9] However, the major difference between LCM and the other "sodium drugs" is that LCM affects the slow-acting sodium channels which is different from the other "sodium drugs" that affect the fast-acting sodium channels. It is suspected that this difference may be the reason why LCM works in patients with PGTCS.[9]

So, what are the important findings of the study by Vossler et al.? While the focus is on PGTCS and the efficacy of LCM as an add-on for the treatment of PGTCs, the implications of this study go beyond that. In my opinion, there are 2 important points for discussion – the novel study design and the reporting on absence and myoclonic seizures. The study design first: instead of the standard comparison of seizure occurrences between placebo and active treatment groups, the investigators resorted to a different design – "time to nth seizure". This design was dictated by a simple fact that PGTCS are relatively infrequent and sometimes difficult to quantify – selecting the standard approach of measuring the difference in seizures per unit of time between placebo and active treatment as the primary outcome measure when counting relatively rare events would actually result in prolonged study participation with patients exposed to a potentially ineffective treatment and a need for recording high numbers of seizures in order to determine whether significant differences between groups exist. The "time to nth seizure" is a novel and forward thinking way of approaching relatively rare events (here: PGTCS) – it reduces the time of taking a treatment that may be ineffective and allows for an overall more rapid data collection. Such trial design was not implemented previously in prospective randomized double-blinded trials but post-hoc analyses of 1 lamotrigine RCT conducted in patients with PGTCS suggest that this may be a viable option for designing RCTs[10]; a somewhat similar approach designed to shorten study participation and duration was used in secondary analyses of perampanel RCT data from focal onset seizure trials (time to pre-randomization monthly seizure count).[11] In the LCM trial discussed here, time to 2nd seizure was implemented – this was dictated by a more rapid titration for LCM when compared to the previously determined 3rd seizure in the above mentioned lamotrigine trial. In the present trial, Vossler and colleagues planned to randomize 250 participants and stop enrolling patients after 125th event was recorded. This resulted in a significant difference in the primary outcome measure with more patients in the active treatment group who did not have the second seizure compared to the placebo group and much longer, on average, treatment duration in the LCM than in the placebo group (143 days vs. 65 days) before the second seizure occurred both of these measures clearly indicating LCM's efficacy in this setting.[1]

The second important point: the results of the analyses of absence and myoclonic seizure data. While these outcomes were secondary and do not affect the Food and Drug Administration (FDA) approval, they provide a very important glimpse into the efficacy of this drug in idiopathic generalized epilepsies as a group of epilepsies rather than only in the PGTCS. The investigators monitored the percentage change in days with absence and myoclonic seizures per 28 days relative to the baseline.[1] While the responses to LCM in patients with absence seizures were numerically similar and possibly better between placebo and active treatment (Supplemental Table 4), the myoclonic seizures were numerically worse in patients receiving the active treatment. These data are very telling – and, in some ways, similar to another "sodium drug" lamotrigine data from the RCT in children with absence epilepsy where lamotrigine was the least effective treatment when compared to ethosuximide and valproate.[6] The findings from this trial in conjunction with the findings from other trials suggest that while "sodium drugs" are (or may be) effective for the treatment of PGTCS, they are less effective (or ineffective) for the treatment of absence and myoclonic seizures and their use in patients with IGEs and seizure types other than PGTCS should be cautious.

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