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[Intervention Review]

Lacosamide add-on therapy for focal epilepsy

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ABSTRACT

Background

This is an updated version of the Cochrane review published in 2015.

Around half of people with epilepsy will not achieve seizure freedom on their first antiepileptic drug; many will require add-on therapy. Around a third of people fail to achieve complete seizure freedom despite multiple antiepileptic drugs. Lacosamide has been licenced as an add-on therapy for drug-resistant focal epilepsy.

Objectives

To evaluate the efficacy and tolerability of lacosamide as an add-on therapy for children and adults with drug-resistant focal epilepsy.

Search methods

We searched the following databases (22 August 2019): the Cochrane Register of Studies (CRS Web), including the Cochrane Epilepsy Group Specialized Register and the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (Ovid, 1946 to 20 August 2019), ClinicalTrials.gov, and the WHO International Clinical Trials Registry Platform (ICTRP), with no language restrictions. We contacted UCB Pharma (sponsors of lacosamide).

Selection criteria

Randomised controlled trials of add-on lacosamide in people with drug-resistant focal epilepsy.

Data collection and analysis

We used standard Cochrane methodology, assessing the following outcomes: 50% or greater reduction in seizure frequency; seizure freedom; treatment withdrawal; adverse events; quality of life; and cognitive changes. The primary analyses were intention-to-treat. We estimated summary risk ratios (RR) for each outcome presented with 99% confidence intervals (CI), except for 50% or greater seizure reduction, seizure freedom and treatment withdrawal which were presented with 95% CIs. We performed subgroup analyses according to lacosamide dose and sensitivity analyses according to population age, whereby data from children were excluded from the meta-analysis.

Main results

We included five trials (2199 participants). The risk of bias for all studies was low to unclear. All studies were placebo-controlled and assessed doses from 200 mg to 600 mg per day. One study evaluated lacosamide in children; all other studies were in adults. Trial duration

ranged from 24 to 26 weeks. All studies used adequate methods of randomisation and were double-blind. Overall, the certainty of the evidence for the outcomes was judged as moderate to high, with the exception of seizure freedom which was low.

The RR for a 50% or greater reduction in seizure frequency for all doses of lacosamide compared with placebo was 1.79 (95% CI 1.55 to 2.08; 5 studies; 2199 participants; high-certainty evidence). The RR for seizure freedom for all doses of lacosamide compared with placebo was 2.27 (95% CI 1.35 to 3.83; 5 studies; 2199 participants; low-certainty evidence). The RR for treatment withdrawal for all doses of lacosamide compared with placebo was 1.57 (95% CI 1.24 to 1.98; 5 studies; 2199 participants; moderate-certainty evidence).

The estimated effect size for most outcomes did not change considerably following sensitivity analysis. For seizure freedom, however, the RR nearly doubled upon the exclusion of data from children (RR 4.04, 95% CI 1.52 to 10.73).

Adverse events associated with lacosamide included: abnormal co-ordination (RR 6.12, 99% CI 1.35 to 27.77), blurred vision (RR 4.65, 99% CI 1.24 to 17.37), diplopia (RR 5.59, 99% CI 2.27 to 13.79), dizziness (RR 2.96, 99% CI 2.09 to 4.20), nausea (RR 2.35, 99% CI 1.37 to 4.02), somnolence (RR 2.04, 99% CI 1.22 to 3.41), vomiting (RR 2.94, 99% CI 1.54 to 5.64), and number of participants experiencing one or more adverse events (RR 1.12, 99% CI 1.01 to 1.24).

Adverse events that were not significant were: vertigo (RR 3.71, 99% CI 0.86 to 15.95), rash (RR 0.58, 99% CI 0.17 to 1.89), nasopharyngitis (RR 1.41, 99% CI 0.87 to 2.28), headache (RR 1.34, 99% CI 0.90 to 1.98), fatigue (RR 2.11, 99% CI 0.92 to 4.85), nystagmus (RR 1.47, 99% CI 0.61 to 3.52), and upper respiratory tract infection (RR 0.70, 99% CI 0.43 to 1.15).

Authors' conclusions

Lacosamide is effective and well-tolerated in the short term when used as add-on treatment for drug-resistant focal epilepsy. Lacosamide increases the number of people with 50% or greater reduction in seizure frequency and may increase seizure freedom, compared to placebo. Higher doses of lacosamide may be associated with higher rates of adverse events and treatment withdrawal. Additional evidence is required assessing the use of lacosamide in children and on longer-term efficacy and tolerability.

PLAIN LANGUAGE SUMMARY

Lacosamide add-on therapy for focal epilepsy

Background

Lacosamide is an antiepileptic drug that can be added alongside other antiepileptic drugs ('add-on therapy') to treat focal seizures (a seizure that starts in one area of the brain). Lacosamide may be beneficial for people who continue to have seizures whilst taking other antiepileptic medication (drug-resistant epilepsy). In this review we studied how well lacosamide works as an add-on for people with drug-resistant focal epilepsy.

Studies

We included five trials with a total of 2199 participants with drug-resistant focal epilepsy. Four trials included adults (aged 16 to 70), and one trial included children (aged 4 to 16). Across the five trials, people were split into two groups and given either lacosamide or a sugar pill (placebo), in addition to their existing antiepileptic medication.

Results

People taking lacosamide were almost twice as likely as those taking placebo to have their number of seizures reduced by 50% or more. People who took lacosamide were also twice as likely to be free of all seizures, compared to those who took placebo. However, people in the lacosamide group were more likely to withdraw from treatment than those in the placebo group, due largely to side effects. People taking lacosamide most commonly reported blurred or double vision, problems with co-ordination, dizziness, drowsiness, nausea, and vomiting.

We separately excluded data from children to study the effect of lacosamide in adults only, to determine whether the inclusion of children affected the results. Adults who took lacosamide were four times more likely to be free of all seizures than adults who took placebo.

Certainty of the evidence

We judged the methods used by the five trials as good, and the evidence found in this review was of moderate to high certainty with the exception of seizure freedom, which was deemed to be low. This means that we are fairly to highly certain that the results we have reported are accurate for most outcomes apart from seizure freedom. We found a difference in results between when adult and children were grouped together compared to when adults alone were studied, suggesting a difference in effect of lacosamide between the two population groups. More research is needed on the long-term effects of lacosamide and to explore how well lacosamide works for children with epilepsy.