

Health Technology Assessment of Lacosamide as Adjunctive Therapy for Partial-Onset Epileptic Seizures

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1. Introduction

Epilepsy is a neurological disorder that disrupts the normal transmission of electrical signals in the brain and is characterised by abnormal electrical neuronal activity resulting clinically in unprovoked recurring seizures. Partial-onset seizures are those that involve only a portion of the brain at seizure onset. The prevalence of epilepsy varies between 4 and 8 cases per 1,000 individuals in developed countries (Hauser, 1990), and partial seizures are the predominant type of epileptic seizures (Kotsopoulos et al., 2002).

Epileptic seizures are associated with significant morbidity, impaired quality of life, mortality, and are a primary driver of hospital admissions and health care costs. A literature review reported an increased mortality risk for people with epilepsy as compared with the general population (Hitiris et al., 2007). A bottom-up, prevalence-based, cost-of-illness analysis estimated the costs of epilepsy from a societal perspective in the 25 European Union member countries, plus Iceland, Norway, and Switzerland (Pugliatti et al., 2007). The estimated total cost of the disease in Europe was € 15.5 billion in 2004, indirect costs related to productivity loss being the single most important cost category (€ 8.6 billion). The total cost per case was € 2,000–11,500 and the estimated cost per European individual was € 33.

Treatment with anti-epileptic drugs (AEDs) is the mainstay of therapy for people with epilepsy and treatment tends to begin with monotherapy (Brodie & Dichter, 1997). First-generation AEDs available before 1980 (e.g. carbamazepine, phenytoin, phenobarbital, valproic acid) are used first-line as monotherapy (Perucca & Meador, 2005). Although many patients respond to their first treatment, more than 1 in 3 patients have seizures despite treatment with AEDs (Schmidt & Gram, 1995). Treatment of refractory epilepsy will move to polytherapy by adding second-generation AEDs available after 1993 (e.g. felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, vigabatrin, zonisamide) to monotherapy regimens (adjunctive therapy). A literature review of systematic reviews reported that second-generation AEDs were effective as adjunctive therapy for refractory epilepsy as compared with placebo (Wilby et al., 2005). Also, a literature review of economic evaluations of second-generation AEDs showed that adjunctive therapy of refractory epilepsy with AEDs appears to be cost-effective (Simoens, 2010).

Several factors inform the choice of the most appropriate treatment regimen in patients requiring adjunctive therapy. Of key importance is that adjunctive therapy for uncontrolled

epilepsy is effective in achieving seizure freedom or reduction in a group of patients who have continued to experience a high seizure burden despite initial treatment for their epilepsy. Given the chronic nature of epilepsy and the requirement for life-long management in many cases, it is important that treatments are tolerable. The ease of use and convenience of the drug also need to be considered. Key positive attributes are treatments that do not require multiple administrations a day and those with flexible dosing options. Clinical guidance also states that the AED treatment strategy should be individualized according to the seizure type, epilepsy syndrome, co-medication and co-morbidity, the individual's lifestyle, and the preferences of the individual, their family and/or those who care for the patient as appropriate (National Institute for Health and Clinical Excellence, 2004).

Lacosamide (Vimpat®, UCB Pharma, Brussels, Belgium) is a second-generation AED which is indicated as adjunctive therapy for partial-onset seizures with or without secondary generalisation in patients from 16 years of age in Europe (European Medicines Agency, 2008). Lacosamide (R-2-acetamido-N-benzyl-3-methoxypropionamide) is a functionalised amino acid. Lacosamide is hypothesized to have a dual mode of action: it selectively enhances slow inactivation of voltage-gated sodium channels and binds to collapsin response mediator protein-2, a protein which is mainly expressed in the central nervous system.

Trials in healthy adults have shown that lacosamide is rapidly absorbed and is predominantly excreted as unchanged lacosamide (Ben-Menachem, 2008). It has an oral bioavailability of approximately 100% and an elimination half-life of around 13 hours. Lacosamide has a low potential for pharmacokinetic interaction. The protein binding is low (<15%), thus reducing the potential for displacement interactions. Also, lacosamide does not influence the pharmacokinetic profile or plasma concentrations of commonly-used AEDs such as carbamazepine or valproic acid. Pharmacokinetic parameters do not differ between genders or single or repeat dose administration (European Medicines Agency, 2008).

Lacosamide is available in five formulations in Europe, an oral tablet (50 mg, 100 mg, 150 mg and 200 mg) and a 15mg/ml syrup, and must be taken twice a day. The recommended starting dose is 50 mg twice a day which should be increased to an initial therapeutic dose of 100 mg twice a day after one week. Depending on response and tolerability, the maintenance dose can be further increased by 50 mg twice a day every week, to a maximum daily dose of 400 mg (200 mg twice a day). The recommended daily dose for lacosamide is 300 mg/day.

The aim of this chapter is to conduct a health technology assessment of adjunctive therapy with lacosamide for partial-onset seizures in adult patients by means of a review of the international literature. The literature study focuses specifically on the safety, tolerability, efficacy, costs, cost-effectiveness and budget impact of lacosamide. The findings may serve to aid local decision-makers in allocating scarce health care resources and to inform the prescribing behavior of physicians.

2. Methods

2.1 Search strategy

Studies were identified by searching PubMed, Centre for Reviews and Dissemination databases (Database of Abstracts of Reviews of Effects, National Health Service Economic

Evaluation Database, and Health Technology Assessments Database), Cochrane Database of Systematic Reviews, and EconLit from January 1999 to March 2011. Additionally, the bibliography of included studies was checked for other relevant studies. Search terms included 'epilepsy', 'refractory epilepsy', 'partial-onset seizures', 'adjunctive therapy', 'add-on therapy', 'anti-epileptic drugs', 'lacosamide', 'adult', 'safety', 'tolerability', 'efficacy', 'effectiveness', 'pharmaco-economics', 'cost', 'cost analysis', 'economic evaluation', 'cost-effectiveness', 'cost-minimisation', 'cost-consequence', 'cost-utility', 'cost-benefit', 'budget impact' alone and in combination with each other.

The literature search included articles published in peer-reviewed journals. Additionally, relevant congress abstracts were identified by searching the congress databases of the European Neurological Society, the American Academy of Neurology, and Outcomes Research Digest (an electronic database of abstracts presented at conferences of the International Society of Pharmacoeconomics and Outcomes Research). Finally, UCB Pharma was contacted for any unpublished studies.

2.2 Selection criteria

The literature review included clinical studies examining the safety, tolerability or efficacy of adjunctive therapy with lacosamide for partial-onset seizures in adult patients. The inclusion of clinical studies was restricted to randomized controlled trials or open-label extension trials. Other study designs (e.g. case studies) were not considered. Cost studies were included if they compared health care and/or other costs of lacosamide and an alternative treatment for partial-onset seizures. Evidence about cost-effectiveness was derived from economic evaluations. An economic evaluation was defined as a study comparing lacosamide with an alternative treatment in terms of both costs and consequences (Drummond et al., 2005) (see Figure 1). Economic evaluations were excluded if treatment of partial-onset seizures did not involve lacosamide or if studies analyzed a single intervention without a comparator.

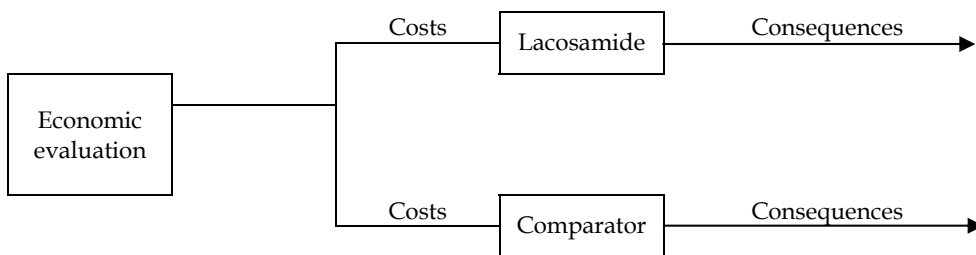


Fig. 1. Economic evaluation of lacosamide

A budget impact analysis explored how a change in the current mix of treatment strategies by the introduction of lacosamide would impact drug spending on partial-onset seizures (see Figure 2).

Studies evaluating intravenous lacosamide were excluded because this article focuses on chronic adjunctive therapy. Literature reviews were searched for original studies, but were not included as such. The review was limited to studies published in English, French, Dutch, or German for practical reasons.

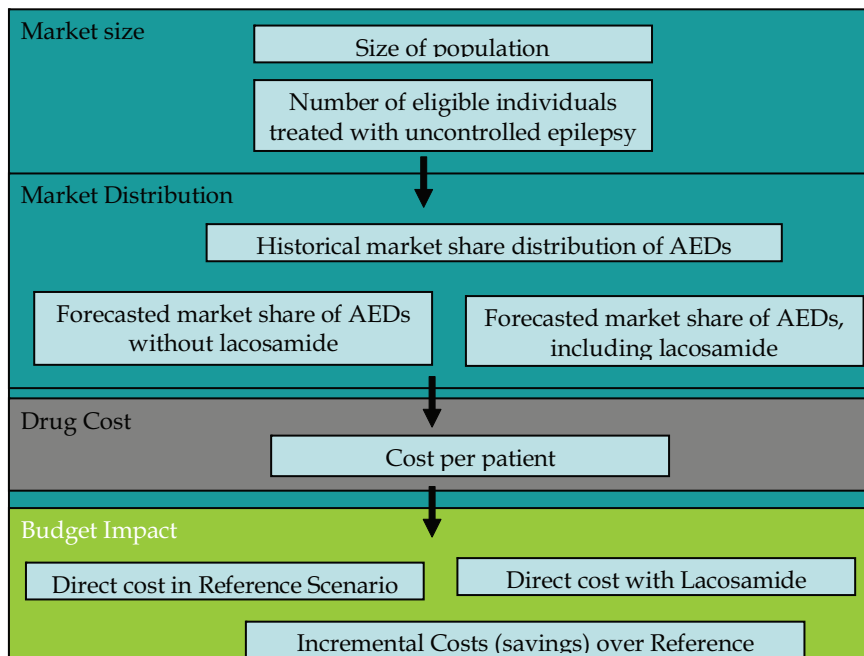


Fig. 2. Budget impact analysis of lacosamide

3. Results

3.1 Search results

Few studies have focused on adjunctive therapy with lacosamide for partial-onset seizures in adult patients: the researcher identified 32 citations, but only nine studies were included in the review: three randomized controlled trials published in peer-reviewed journals¹⁴⁻¹⁶, three open-label extension studies published as abstracts (Ben-Menachem et al., 2009; Rosenfeld et al., 2009; Faught et al., 2010; Husain et al., 2010), one economic evaluation published in a peer-reviewed journal (Bolin et al., 2010), and two economic evaluations published as abstracts (one of which also included a budget impact analysis) (Simoens et al., 2010; Soini et al., 2009). Studies were excluded because of one or more of the following reasons: disease other than refractory epilepsy; study not involving lacosamide; study of intravenous lacosamide; study of pharmacodynamic and/or pharmacokinetic profile of lacosamide; literature review rather than original study; case study.

3.2 Safety, tolerability and efficacy

Three randomised, multicentre, double-blind, placebo-controlled trials have been carried out on the efficacy of adjunctive therapy with lacosamide: phase IIb trial 667, phase III trial 754 and phase III trial 755 (Ben-Menachem et al., 2007; Chung et al., 2010; Halasz et al., 2009). The three trials were similar in design and patient baseline characteristics. All patients included in these pivotal trials were patients who had uncontrolled epilepsy despite previous treatment with at least two other AEDs (concurrently or sequentially) and who were actively treated with concomitant AEDs as standard therapy. The most

commonly used concomitant AEDs were carbamazepine, levetiracetam and lamotrigine. The primary objective of these trials was to evaluate the efficacy of lacosamide as adjunctive therapy following treatment failure with at least two other AEDs and co-administered with one or two other AEDs (trial 667) or up to three other AEDs (trials 754 and 755) in patients with uncontrolled partial-onset seizures. The secondary objective was to evaluate the safety of lacosamide. Patients were randomised to a 200 mg, 400 mg or 600 mg daily dose of lacosamide or placebo.

Outcomes were measured in terms of the reduction in seizure frequency, 50% responder rate and seizure-free status. Responder rate was assessed as a reduction in partial-onset seizure frequency of at least 50% from baseline to maintenance phase. Seizure-free status was determined for patients who completed the maintenance phase with zero seizures. Improvements in quality of life, patient function and health status were assessed via secondary endpoints including the Quality of Life Inventory In Epilepsy (QOLIE-31) scale, the Seizure Severity Scale (SSS) and the Patient Global Impression of Change (PGIC) scale.

Patients treated with lacosamide 400 mg/day and 600 mg/day in trial 667 showed a statistically significant reduction in seizure frequency at maintenance endpoint (after 18 weeks) as compared with placebo (400 mg/day: $p = 0.0023$; 600 mg/day: $p = 0.0084$). Patients in trial 754 and 755 also displayed a statistically significant reduction in seizure frequency when treated with lacosamide as compared with patients treated with placebo (Trial 754: 400 mg/day $p = 0.0078$, 600 mg/day $p = 0.0061$; Trial 755: 200 mg/day $p = 0.0223$, 400 mg/day $p = 0.0325$). Lacosamide was associated with a significantly greater median percent reduction in seizure frequency from baseline at a dose of 400 mg/day and 600 mg/day across trials. In trial 755, lacosamide 200 mg/day was associated with a significantly greater median seizure reduction as compared with placebo ($p = 0.04$). Treatment with lacosamide (200–600 mg/day) gave higher responder rates as compared with treatment with placebo. The differences were generally significant as compared with placebo for patients treated with lacosamide 400 mg/day and lacosamide 600 mg/day.

A pooled analysis of the trial data suggested that the median percent reduction in seizure frequency per 28 days from baseline to maintenance period amounted to 18.4% for placebo, 33.3% for lacosamide 200 mg/day ($p < 0.01$), 36.8% for 400 mg/day ($p < 0.001$), and 39.4% for 600 mg/day. The percentage of patients attaining a reduction in seizure frequency of at least 50% was 22.6% with placebo, 34.1% with lacosamide 200 mg/day ($p < 0.05$), 39.7% with lacosamide 400 mg/day ($p < 0.001$), 39.6% with lacosamide 600 mg/day. The median percent reduction in seizure frequency and the percentage of patients attaining a reduction in seizure frequency of at least 50% did not vary depending on the number of previously used AEDs. Patient responders with more than 50% seizure reduction in the lacosamide treatment groups experienced significant improvements in QOLIE-31 and SSS scores as compared to baseline ($p < 0.05$ for all comparisons of responders to non-responders) (Cramer et al., 2010). The largest improvements were gained for quality-of-life scores including the QOLIE-31 subscales 'seizure worry' and 'social functioning', as well as the SSS overall score. With respect to PGIC, more than 80% of lacosamide responders reported an improved health status. Finally, there seemed to be a dose-responsive trend for seizure freedom rates: 2.7%, 3.3% and 4.8% for lacosamide 200, 400 or 600 mg/day as compared with 0.9% for placebo (French et al., 2009).

The most common drug-associated treatment-emergent adverse events in the lacosamide treatment arms of the pivotal trials were dizziness and nausea (Gil-Nagel et al., 2009). Headache was also commonly reported with lacosamide. The incidence of adverse events was generally higher in the forced titration phase as compared with the maintenance phase,

indicating a reduction in these adverse events over time. Forced titration does not reflect usual clinical practice. Adverse events were reported to be of mild or moderate intensity. Three open-label extension studies of the pivotal trials explored the long-term safety, tolerability and efficacy of lacosamide (see Table 1) (Ben-Menachem et al., 2009; Rosenfeld et al., 2009; Faught et al., 2010; Husain et al., 2010). Long-term treatment with lacosamide produced a sustained efficacy in and was generally well tolerated by patients suffering from partial-onset seizures. The incidence of adverse events, as well as vital signs and clinical laboratory and ECG findings, among patients taking lacosamide were similar to those reported with short-term use (O'Brien, 2010).

3.3 Costs

No cost study comparing lacosamide with an alternative treatment for partial-onset seizures was identified in the literature. It is difficult to determine the cost implications of adjunctive therapy with lacosamide on patients, the health care system and society. Therefore, Table 1 proposes the major items that need to be considered when calculating costs from a societal perspective. With respect to direct health care costs, current treatment strategies include pharmacotherapy with AEDs throughout life, surgery, and alternative measures – usually palliative – such as vagus nerve stimulation. A study also needs to consider the cost (and clinical) implications of the fact that AED therapy may affect co-morbid disease, that drugs used to treat co-morbid diseases may influence the seizure threshold, that the toxicity of AEDs may be influenced by a co-morbid condition and that clinically relevant drug–drug interactions can arise from the co-administration of AEDs with drugs used to treat co-morbid diseases (Zaccara, 2009). In addition to direct health care costs, future studies need to elicit direct non-health care costs of transportation to health care professionals and indirect costs. With respect to the latter, attention needs to be paid to calculating the indirect costs of days lost to education, costs of reduced ability to carry out normal everyday activities, and the costs of productivity loss of patients and of family/friends who care for patients.

Medication	Direct health care costs		Direct non-health care costs	Indirect costs of patients and carers
	Health care providers	Other		
Anti-epileptic drugs	General practitioner	Diagnostic tests	Transportation to health care provider	Absence from work
Antidepressants	Nurse	Accident and Emergency visit	Child care costs	Reduced productivity at work
Antipsychotics	Pharmacist	Hospital stay	Home adaptations	Time lost from education
Benzodiazepines	Neurologist	Surgery		Reduced ability to carry out usual daily activities
Cardiovascular drugs		Palliative care		
Antineoplastic drugs		Home health care services		
Antibiotics		Alternative medicine		
Antiretroviral drugs				
Interferons				

Table 1. Items to be considered in cost studies of lacosamide

3.4 Cost-effectiveness

Three economic evaluations used a similar design to determine the cost-effectiveness of lacosamide from the health care payer perspective in Sweden, Finland and Belgium (Bolin et al., 2010; Simoens et al., 2010; Soini et al., 2009). These studies compared standard AED therapy plus lacosamide with standard AED therapy alone in treating partial-onset seizures with or without secondary generalization in epilepsy patients from 16 years who are uncontrolled on current treatment with at least two AEDs.

A decision-analytic model simulated the treatment pathway of a hypothetical patient cohort over two years. Data about health state probabilities, seizure frequency and utility values were taken from the pivotal trials or from the literature. For instance, the models used a probability of a seizure reduction of 0.368 and a probability of withdrawal due to non-response of 0.632 in patients treated with standard AED therapy plus lacosamide. Similarly, the probability of a 50% seizure reduction was 0.194 and the probability of withdrawal due to non-response was 0.806 in patients treated with standard AED therapy alone. Health care costs included costs of drugs, physician visits, laboratory tests, and hospitalization. The two consequence measures considered were the number of seizures and quality-adjusted life years because AED treatment primarily impacts seizure frequency and health-related quality of life. As the models did not take into account adverse events, the costs associated with adverse events associated with AED treatment was not considered when calculating the cost-effectiveness of lacosamide. Also, the models did not consider mortality. This is because the trials 754 and 755 did not report mortality rates in this specific population of uncontrolled epileptic patients and because of the limited time period of the models of two years (Chung et al., 2010; Halasz et al., 2009). The robustness of results was tested by means of deterministic and probabilistic sensitivity analyses.

The Swedish economic evaluation found that the incremental cost per seizure avoided amounted to € 156 and that the incremental cost per quality-adjusted life year gained was € 27,641 at 24 months (Bolin et al., 2010). If indirect costs of productivity loss would be considered, standard therapy plus lacosamide would be more effective and less expensive than standard therapy alone. According to the Finnish economic evaluation, standard therapy plus lacosamide led to a reduction of 8.92 seizures, an increase of 0.041 quality-adjusted life years, and a cost increase of € 831 per patient as compared with standard therapy alone over a 24-month period (Soini et al., 2009). Using a willingness to pay of € 30,000 and € 50,000 per quality-adjusted life year, the probability of standard therapy plus lacosamide being cost-effective was 74.4% and 87.7%, respectively. The Belgian economic evaluation observed that standard therapy plus lacosamide is more effective and less expensive than standard therapy alone under the two consequence measures considered and under the four time periods considered (6, 12, 18 and 24 months) (Simoens et al., 2010). Extensive sensitivity analyses demonstrated that these results were robust to changes in input parameters.

3.5 Budget impact

In addition to cost-effectiveness, the Finnish study calculated the budget impact of lacosamide from the health care payer perspective (Soini et al., 2009). The analysis compared the “world with lacosamide” to the “world without lacosamide” and calculated how a change in the mix of AEDs used to treat uncontrolled epilepsy would impact drug spending during 2008-2012. Data on the number of patients, AED market shares and unit costs were taken from Finnish sources. The authors applied the conservative assumption of using

generic drug prices in the analysis. It should be noted that this analysis focused on drug costs only and did not consider the fact that lacosamide reduces costs of seizure management and withdrawal, as demonstrated by the economic evaluations (Bolin et al., 2010; Simoens et al., 2010; Soini et al., 2009). The results indicated that the expected annual drug budget increase due to the introduction of lacosamide would rise to € 232,600 in 2012. Expressed as a proportion of the annual epilepsy budget, the introduction of lacosamide would increase the budget by 2.23% in 2012.

4. Discussion

Insufficient epilepsy treatment in terms of seizure control may have a significant negative impact on patients' quality of life and represents a substantial economic burden for patients and society. There is an unmet need for treatment options for uncontrolled patients with partial-onset seizures. Lacosamide, a second-generation AED, is indicated for the treatment of such patients. This study has drawn on the international literature in order to provide a comprehensive review of various aspects of pharmacotherapy with lacosamide (i.e. safety, tolerability, efficacy, costs, cost-effectiveness and budget impact). Although the review considered both published articles and congress abstracts, the evidence on lacosamide was limited and studies suffered from a number of methodological limitations. The evidence, limitations and avenues for future research are discussed in the following paragraphs.

The safety, tolerability and efficacy of lacosamide as an adjunctive therapy in partial-onset seizures have been demonstrated across three randomised, placebo-controlled, double-blind, multicentre trials in over 1,300 adults with epilepsy. Patients receiving lacosamide demonstrated a significant reduction in seizure frequency and significantly higher 50% response rates in comparison with patients who received placebo. Furthermore, open-label extension studies showed that long-term treatment with lacosamide produced a sustained efficacy in and was generally well tolerated by patients.

The existing clinical evidence has investigated the efficacy of lacosamide under 'ideal conditions' rather than its effectiveness in real-life practice. Also, populations studied in clinical trials may not reflect populations observed in clinical practice. There is a need for post-marketing surveillance studies that conduct head-to-head comparisons of different combinations of AEDs including lacosamide. Although analyses based on cohort studies, case-control studies, or before-and-after studies may suffer from a number of biases and do not always establish a cause and effect relationship, such studies would provide information about the safety, tolerability, and effectiveness of lacosamide in real-life practice.

Existing economic evaluations have drawn on similar decision-analytic models to investigate the cost-effectiveness of lacosamide in three different countries. The evidence indicated that in patients who are difficult to treat with currently reimbursed treatment alternatives, standard AED therapy plus lacosamide is likely to constitute a cost-effective alternative. The budget impact of introducing adjunctive therapy with lacosamide is also likely to be limited. Uncertainty surrounds the cost-effectiveness of lacosamide because economic evaluations derived efficacy estimates from short-term trial data, thus necessitating extrapolation; there are few head-to-head comparisons of the efficacy of AEDs; and there are few data on utility values associated with epileptic health states.

There is a need for more economic evaluations of adjunctive therapy of partial-onset seizures with lacosamide. Studies need to be carried out that collect primary long-term data on effectiveness and cost-effectiveness of lacosamide as compared to other available AEDs.

Further research needs to assess quality of life, using preference-based measures of outcomes that generate appropriate utilities for economic evaluation.

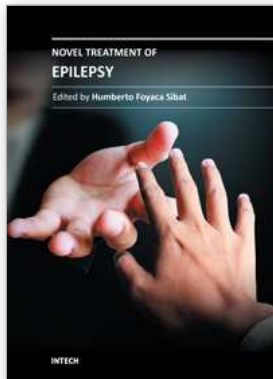
5. Conclusion

Because of the complexity of epilepsy diagnosis and management, physicians should be presented with a wide choice of therapeutic options in order to individualize AED treatment to each patient. In light of the available evidence, lacosamide needs to be considered as a safe, efficacious and cost-effective option as adjunctive therapy for patients with partial-onset epilepsy with or without secondary generalization who are uncontrolled having previously used at least three AEDs. However, these results need to be validated by studies that explore the impact of lacosamide in real-life clinical practice.

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Epilepsy continues to be a major health problem throughout the planet, affecting millions of people, mainly in developing countries where parasitic zoonoses are more common and cysticercosis, as a leading cause, is endemic. There is epidemiological evidence for an increasing prevalence of epilepsy throughout the world, and evidence of increasing morbidity and mortality in many countries as a consequence of higher incidence of infectious diseases, head injury and stroke. We decided to edit this book because we identified another way to approach this problem, covering aspects of the treatment of epilepsy based on the most recent technological results *in vitro* from developed countries, and the basic treatment of epilepsy at the primary care level in rural areas of South Africa. Therefore, apart from the classic issues that cannot be missing in any book about epilepsy, we introduced novel aspects related with epilepsy and neurocysticercosis, as a leading cause of epilepsy in developing countries. Many experts from the field of epilepsy worked hard on this publication to provide valuable updated information about the treatment of epilepsy and other related problems.

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