Analysis of Pregabalin and Lacosamide Using the Post-Marketing Antiepileptic Drug/Device Survey.
Analyse de la prégabaline et lacosamide utilisant l'enquête post marketing médicament appareil antiépileptique.

Jeorge L. Morris , Johnson, EP[b]
Aurora Epilepsy Center, Aurora St Luke's Medical Center, (USA)
University of Wisconsin Milwaukee, Milwaukee, WI
Email: george.morris@epilepsycarespecialists.com
No disclosure to be declared.

Résumé

Les patients atteints de l'épilepsie ont bénéficié d'un certain nombre de nouveaux médicaments dans le traitement des crises partielles. En plus d'être de nouvelles options de traitement, ces médicaments ont également élargi la population cibles de ces traitements médicamenteux. Cette expansion de la population traitable de groupes particuliers tels que les femmes enceintes, les enfants et les personnes âgées a poussé les médecins à faire des choix entre les médicaments disponibles sur la base de perception de la sécurité. Quelques informations-clés qui pourraient guider le choix d'un médecin ne sont généralement pas collectées lors des essais de médicaments initiaux. Nous présentons ici une étude réalisée pour comparer l'utilisation et l'efficacité globale de deux médicaments, la Prégabaline et la Lacosamide. Ils furent administrés chez 158 patients pour la Prégabaline et 137 patients pour Lacosamide. La fréquence initiale moyenne des crises partielles complexes (CPC) pour les patients mis sous Prégabaline était de 6 crises par mois et 5,5 crises par mois pour les patients mis sous Lacosamide. Après six mois, la fréquence des CPC a diminué à 3,8 et à 4 par mois pour Prégabaline et Lacosamide respectivement. Toutefois, l'évaluation globale du patient ne semble pas refléter l'efficacité comparée de ces deux médicaments; avec une évaluation meilleure ou encore plus meilleure de survenue de crises chez 32% des patients mis sous Prégabaline et 51% des patients mis sous Lacosamide. Les évaluations globales d'un meilleur ou encore plus meilleur résultat étaient de 11 % pour la Prégabaline et 24 % pour la Lacosamide. Ces résultats ne sont pas ce que l'on pourrait s'attendre compte tenu de la réduction de la fréquence observée des CPC. Aussi inattendu, compte tenu de la répartition mondiale de l'évaluation, était le taux de rétention de 88% pour Lacosamide et de 95% pour la Prégabaline respectivement. Une étude plus approfondie de la relation entre l'évaluation globale des patients, la fréquence des CPC , et les taux de rétention peut être justifiée dans des recherches ultérieures.
Mots-clés: Epilepsie- Traitement- Evaluation- Lacosamide- Prégabaline.

Abstract

The epilepsy community has been the fortunate recipient of a number of new drugs that have come onto the market for the treatment of partial seizures. In addition to being new treatment options, these medications have also expanded the population eligible to receive drug treatment. This expansion of the treatable population to special groups such as the elderly, pregnant women and children has caused doctors to make choices between the available medications based on perceptions of safety. Some key information that could guide a physician's choice is not typically collected during initial medication trials. We present here a study done to compare the usage and global effectiveness of two medications, Pregabalin and Lacosamide. 158 patients were administered Pregabalin and 137 patients were administered Lacosamide. The average initial frequency of complex partial seizures (CPS) for patients starting Pregabalin was 6 per month and 5.5 per month for patients starting Lacosamide. After six months, CPS frequency decreased to 3.8 and 4 per month for Pregabalin and Lacosamide respectively. However, the patient global assessment did not seem to reflect the comparative effectiveness of the two medications; with assessments of better or much better occurring in 32% of Pregabalin patients and 51% of Lacosamide patients. The global assessments of better or much better were 11% for Pregabalin and 24% for Lacosamide. These results are not what one might expect given the reduction in CPS frequency observed. Also unexpected, given the global assessment distribution, was the 88% retention rate for Lacosamide and the 95% retention rate for Pregabalin respectively. Further study into the relationship between the patient global assessment, CPS frequency, and retention rates might be warranted in further research.
Keywords: Epilepsy- Treatment- Assessment- Lacosamide- Pregabaline.

Introduction

Patients with epilepsy number in the millions, with 150,000 to 200,000 new cases diagnosed in the United States each year. The prevalence of patients with recurring seizures is approximately 1% in the U.S. While the majority of patients will achieve seizure freedom with therapy, 30-40% of patients will continue to have seizures even with the use of antiepileptic medication. But a primary goal of treatment in these cases is not to stop seizure activity altogether, but to reduce the frequency at which it occurs. To this end, a number of relatively new options have become available in the last 18 years.

The Epilepsy community has recently been the fortunate recipient of many new medications for the treatment of complex partial seizures. Eight new antiepileptic

medications were introduced between 1993 and 2004, which raised the number of available medications from 5 to 13. New antiepileptic drugs (AEDs) are continually being developed and brought to market faster and faster, and the release of these drugs has now created previously unseen challenges for the clinician with regards to making an informed decision as to how to optimize the outcomes of drug effectiveness, a patient's global assessment of the medication, and retention rates. Practicing physicians, while happy to have treatment options must now try to chart an optimized treatment course while lacking information about how to best administer some of these new drugs to groups of patients that demand special attention and caution. While caution and attention are always an important component of the prescription of powerful chemicals such as AEDs; it is especially important in vulnerable and less robust patient populations such as women in gestation, children and the elderly.

However, there are limitations in the available information about the newly released antiepileptic medications that could hinder a practicing physician's ability to successfully incorporate these safety precautions into their recommended treatment course. There is a plethora of important information which a physician would use to guide their decision about a particular patient's treatment course that is not typically amongst the data collected during initial medication trials. Information such as: Interactions with other medications, teratogenicity, psychiatric co-morbidities, and medical co-morbidities are restricted from initial trials to assure the uniformity of treatment groups. Also, adverse events collected in short time periods and with forced titration to fixed doses do not mimic patient care. Rare side effects are not seen and pharmacology information may not emphasize the best approach to dosing and potential interactions. But restricting the subject population to assure uniformity of treatment groups like this creates a problem; that is the treated patient population might not be represented by the sample population in the initial drug trials.

This problem, of the characteristics of the sample population of experimental trials not matching those of the treatment population is not a phenomenon specific to clinical trials for new antiepileptic medications. With the age of big data having officially dawned, researchers from academia to industry in all areas of research can now start to consider novel methods for studying phenomena previously out of the reach of a controlled scientific environment. In the case of epilepsy, we hope to see a multi-institutional data management tool get developed that will help scientists and clinicians dig deeper at the question of how to best deliver patient care, including use of the variety of available AEDs. To this end, a database tool such as the one that has been described could store reams of information that potentially even of low quality could help researchers draw inferences about different aspects of epilepsy care and question the validity of generally accepted care practices that don't seem to have much empirical science to back them. Mapping out the chasm of information between controlled experimental environments and actual medical care is a problem that can only be tackled with the aid of a large database system such as the one we hope to see developed.

However, even with such a large computational resource as a researcher's finger tips; the extent to which the outcomes of research trials mimic average outcomes in practice is still not easy to quantify and hard to predict.. The first steps in the quantification of this comparison between outcomes in clinical trials and outcomes in practice must be to deliver accurate information about the actual use of these new antiepileptic medications by practicing physicians. It is also important to assess a patient's overall experience of the medication in comparison to the drug's effectiveness at reducing seizures. For a long it has been thought that the retention rate of an AED was a good indicator of the drug's effectiveness. As part of the effort to use all of the computational resources to our advantage in delivering the best medical care available, it is vital that we collect overwhelming evidence to back up this "common sense" notion that retention rates serve as good indicators of drug effectiveness.

It is our hope that future studies could potentially use these preliminary results we have generated to start to understand the nature of any gaps that might exist between the effectiveness of a drug at reducing seizures and the overall experience of the patient.

Objective

Our aim was to assess the use of new antiepileptic drugs (AEDs) in everyday clinical practice outside of the research setting using an industry-independent design. Patient characteristics, titration rates, associated diseases, and other clinical trial parameters may differ from those encountered by physicians in practice. With this in mind, we set out to make observations that compare whether the effectiveness of two AEDs, Lacosamide and Pregabalin, at reducing CPS frequency is consistent with a patient's global assessment of the drug's effectiveness and the rate of retention.

Patients and Methods

Patients, who were recently started on Pregabalin or Lacosamide at the Regional Epilepsy Center, were identified and deemed eligible by the treating physician or clinic staff. To add a new subject into the database, study personnel created a subject profile by entering the subject's name, medical record number and clinical site. Data collection could be completed using either the paper form or entered directly into the website. The paper forms were available as PDF files on the website. Study personnel completed the study forms by abstracting clinically relevant information from the subject's medical chart. Data collection occurred retrospectively (i.e. after both of the initial and follow-up clinic visits had taken place) and did not affect the subject's treatment course. A six-moth follow-up chart review was completed for all subjects. Information was abstracted and entered into the database after the subject was seen for a regular clinic visit

at least six-months after starting one of the medications of interest. Once the six-month medical chart review was entered into the database, the subject was considered complete.

Separate data collection forms and website application were created for Pregabalin and Lacosamide. Versions of the initial and follow-up forms for Pregabalin and Lacosamide were included as a reference. All Identifiers were removed prior to analysis. De-identified data were released in aggregate form to participating investigators upon request. Qualitative comparisons were conducted of the initial and follow-up subject data. The data was utilized to generate reports of demographic information, seizure frequency, frequency of adverse events and the number of serious adverse events, if any. A demographic sub-analysis was completed to determine the presence of specific trends within select populations (i.e. children, elderly, pregnant women).

Results

A total of 295 patients were entered into the database; 137 Lacosamide, 158 Pregabalin with the average age of the patient being 43 and an average of onset being 17.3 years old. Most of the patients treated had localization related epilepsy syndromes (230) with a sparse number of primary generalized syndromes (22). The average initial seizure frequency of patients surveyed on Pregabalin and Lacosamide were 6 complex partial seizures (CPS) and 5.5 CPS per month, respectively (figure 1).

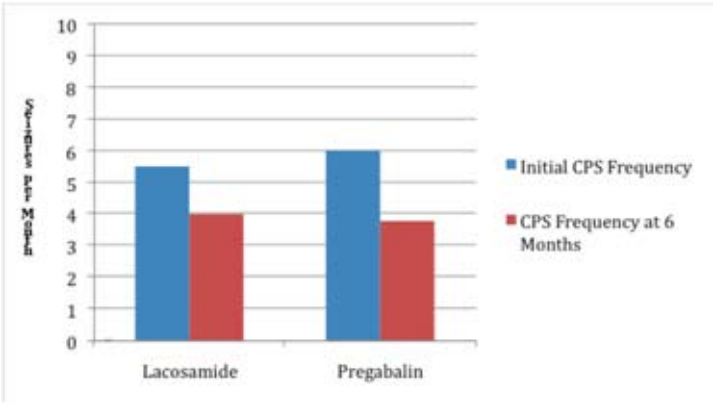

Figure 1: Complex Partial Seizure Frequency.

Average dose intake for Pregabalin and Lacosamide were 329mg and 370mg per day respectively. The final CPS frequency at 6 months was 3.8 and 4 for Pregabalin and Lacosamide respectively. Seizure and global assessment of patients surveyed after their 6 month follow up showed a slight discrepancy with regards to each other. Seizure assessments of better or much better occurred in 32% of Pregabalin patients and 51% of Lacosamide patients. However, global assessments of better or much better status were 11% for Pregabalin and 24% for Lacosamide. Interestingly, the retention rate for Pregabalin and Lacosamide was 95% and 88% respectively (figure 2).

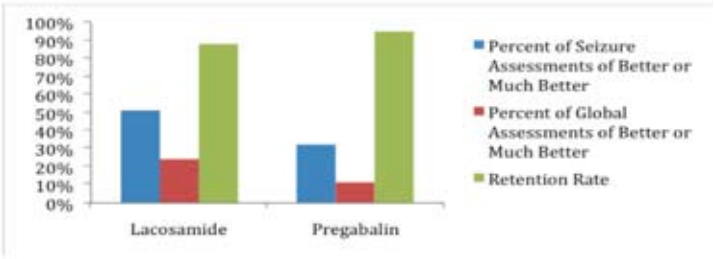

Figure 2: Distribution of Seizure and Global Assessments of Better or Much Better vs. Retention Rate.

Discussion

The study demonstrated potential to enroll patients starting new seizure medications, and followed patients over a six month period; documenting their general global and seizure outcomes (figure 3 and 4).

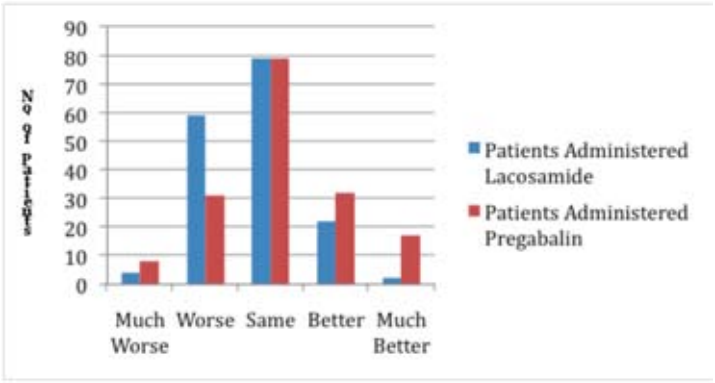

Figure 3: Global Assessment.

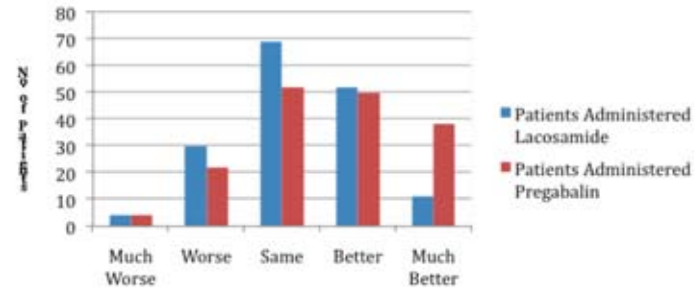

Figure 4: Seizure Assessment.

This study clearly documents that there are seizure reduction benefits in the management of epilepsy with Lacosamide and Pregabalin (figure 5 and 6).

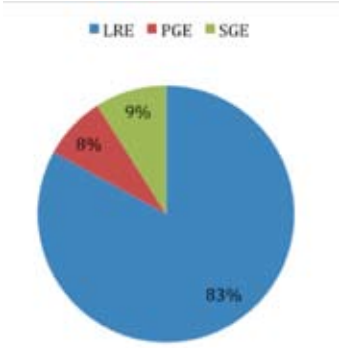

Figure 5 : Pregabalin.

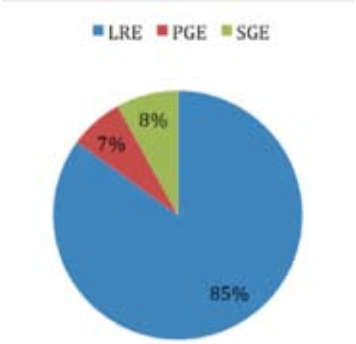

Figure 6: Lacosamide.

Patients report a significant reduction in their seizures and some report improvement in their global status. This is consistent with results of the clinical trials for these medications.

The most commonly used concomitant medications were present in the study, and while no statistical significance can be drawn from the percentages there appears to be no specific combination frequently of AEDs prescribed (figure 7).

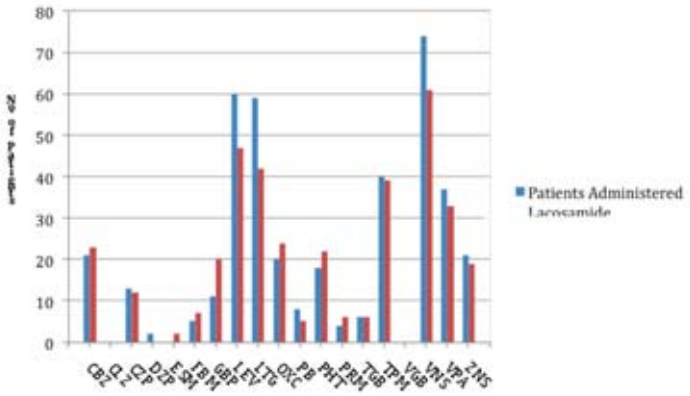

Figure 7: Concomitant Medications.

The interesting aspect of these results show what appears to be a slight disconnect between reports of seizure reductions and global assessments. Seizure reductions are clearly present, but the majority of patients do not report their overall quality of life to be better. They also do not appear to report their seizures to be overall better as well. A potential explanation could be that the magnitude of the seizure reduction simply falls below the threshold for their seeing quality-of-life improvements. A second disconnect is more disturbing. These patients demonstrated an overall report of no significant improvement in quality of life or of seizure frequency and yet retention rates are quite high. A predominant "common sense" belief in the assessment of the success of medications like AEDs has been that retention on the treatment at 6 months is reflective of a successful intervention. This data would potentially argue against that point. Among possible explanations for persistence on the medication despite a significant improvement would be that in comparison to the prior therapy, these medications seemed more affective while still not perfect. Other factors could influence their desire to move to another medication such as the absence of viable alternative medications. Also, other inducements might exist to remain on the medication such as a favorable status financially with perhaps lower patient costs for these 2 medications when compared to other medication choices.

Enrollment from a single site in this circumstance has limitations. Referral patterns into a comprehensive epilepsy clinic are not likely to be representative of the larger seizure population. These patients have potentially been exposed to many medications prior to referral to a comprehensive epilepsy program. Subjects entering this clinic likely receive a more detailed clinical intervention due to additional resources dedicated to epilepsy clinics. It would be preferable to have patients enrolled from a broader community perspective to sample a more representative epilepsy patient community.

The development of this application as a web based system is specifically designed for the next step in the process of expanding long term trials to a broader community of epilepsy patients. The next step in the process would be establishing a web-based presence and engaging the broader community of neurologists in a community patient enrollment. Acquiring patient outcomes from other locations and other clinical circumstances would markedly enhance the comparative effectiveness component of this research. What might be of particular interest to the global epilepsy community is the acquisition of patient data on a worldwide basis into a single database which practitioners in individual countries could utilize and potentially compare, contrast, and learn from their experiences in contrast to those of communities of similar patient situations. These enrollments could be particularly of value to health care systems with limited resources for individual comparative affectedness research.

Conclusions

Pregabalin and Lacosamide were effective in reducing seizures and well tolerated based on high retention rates. However, patient global assessments and patient assessments of overall seizure reduction effectiveness do not reflect this high retention rate. Further study into the relationship between all of these outcome metrics should studied further.