ISSN: 0067-2904

Levetiracetam Monotherapy in Treatment of Generalized Epilepsies Based on Machine Learning Models

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Received: 16/10/2024 Accepted: 13/5/2025 Published: 30/5/2026

Abstract

Epilepsy is recurrent unprovoked seizures with incidents of about 50 new cases per year per 100,000 people. Generalized seizures indicate abnormal electrical discharges starting synchronously from both sides of the cerebral hemispheres and spreading to the other neuronal brain networks. This study included an analysis of 200 diagnosed generalized epilepsies patients aged from 14 to 50 years old. The male-to-female ratio was 2:3, in which 40% were males and 60% were females . From Erbil Hospital, doctors collected the data during 2018-2024 manually from the outpatient clinic. The study aimed to test Levetiracetam (LEV) drug on 200 patients to predict its effectiveness in the treatment of generalized epilepsies and determine the side effects of LEV by using machine learning models. The results showed that LEV could become the first-line monotherapy and be effective for the treatment of generalized epilepsies in patients aged 14-50 years regardless of sex. It has fewer side effects than the old-generation antiepileptics. Accordingly, machine learning models were applied like support vector machine (SVM), which could achieve good results in terms of accuracy and F1_score of 0.935 and 0.903 for patients who suffer from side-effects of Levetiracetam tablet.

Keywords: Levetiracetam (LEV), Generalized Epilepsy (GE), Monotherapy, Machine Learning, SVM.

استخدام التعلم الآلي في العلاج الأحادي لعقار الليفاتيراسيتام للصرع المعمم

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الخلاصة

الصرع عبارة عن نوبات متكررة غير مبررة يحدث بمعدل 50 حالة جديدة سنويا لكل 100000 نسمة. تعني النوبات المعممة بدأ الأنشطة الكهربائية غير الطبيعية في وقت واحد من نصفي الكرة المخية الأيمن والأيسر ثم انتشارها إلى شبكات الخلايا العصبية الدماغية الأخرى. تتضمن هذه الدراسة تحليل 200 مريض من الصرع المعمم التي تتراوح أعمارهم بين 14 و 50 عامًا. كانت نسبة الذكور إلى الإناث 2:3 حيث كانت 40٪ منهم من الذكور و 60٪ من الإناث. تم جمع البيانات من قبل الأطباء خلال الفترة الواقعة بين 2018–2024 يدويًا من العيادة الخارجية في مستشفى أربيل. استهدفت الدراسة اختبار عقار ليفاتيراسيتام (LEV)

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على 200 مريض وتوقع الآثار الجانبية لهذا الدواء باستخدام نماذج التعلم الآلي. قد يكون LEV دواءً فعالاً للعلاج الأحادي لمرض الصرع المعمم في الفئات العمرية الواقعة بين 14–50 عامًا والتي تتضمن كلا الجنسين. إن لهذا الدواء آثار جانبية قليلة مقارنة بمضادات الصرع القديمة، ولهذا الغرض استخدمنا نماذج التعلم الآلي كآلة دعم المتجهات SVM التي يمكن أن تحقق نتائج جيدة من حيث الدقة والـF1_score 0.935 من المرضى الذين يعانون من الآثار الجانبية لأقراص الليفاتيراسيتام.

1. Introduction

Epilepsy is a long-term brain disease represented by repeated unprovoked seizures. It is one of the most common neurologic disorders, with incidences of about 50 new cases per year per 100,000 persons [1]. A seizure is an abrupt and temporary occurrence of signs or symptoms due to abnormal bursts of electrical activity of neuronal cells in the brain [2]. Epilepsy could occur at any age; however, recent data found that the majority of patients with epilepsy are aged between 10 and 30 years [3] [4].

Epilepsy is regarded as the fourth most common neurological disease [5]. According to WHO, as of 7 February 2024, more than 50 million people worldwide have epilepsy. Generally, the causes of epilepsy are unknown in 50% of cases, according to Epilepsy (who.int). About 60%–70% of patients with seizures are controlled with appropriate antiseizure medicines [1] [6]. Therefore, decreasing the rate of misdiagnosis and underdiagnosis of epilepsy is important. Epilepsy diagnosis requires at least two attacks of unprovoked seizures that occur more than twenty-four hours apart.

A lot of factors are playing a role in the categorization of epilepsy; these factors include the patient's age at onset, type of seizure, history of epilepsy in the family, electroencephalogram (EEG), and magnetic resonance imaging (MRI) findings of the brain [2]. Seizure pattern and its frequency contribute to the quality of life (QOL) of epilepsy patients [7]. The International League Against Epilepsy (ILAE) in 2017 published an operational categorization of seizures (Figure 1). Learning this categorization is helpful in the diagnosis and treatment of seizures and epilepsies [8] [9] [10] [11].

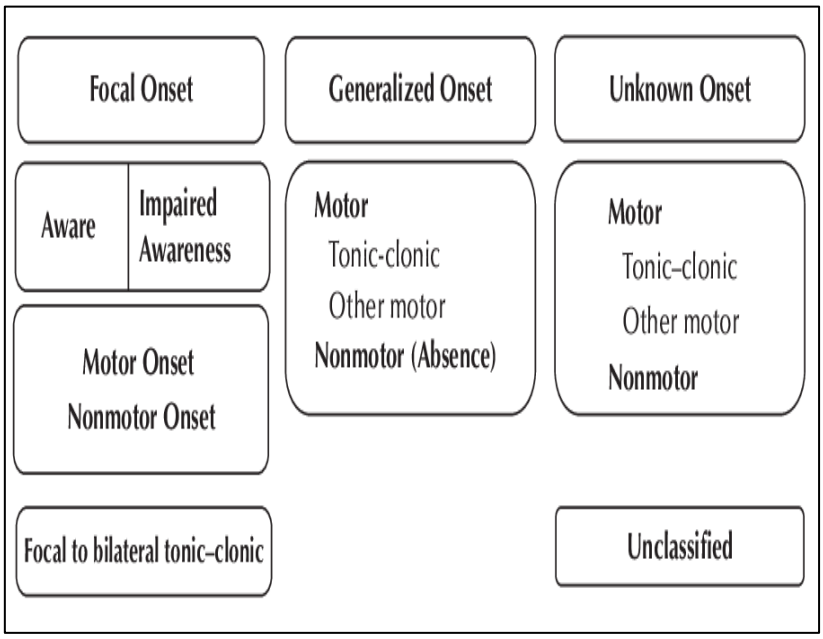

Figure 1: ILAE 2017 seizure types classification.

Generalized epileptic seizures indicate that abnormal electrical impulses started coincidentally from both sides of the cerebral hemispheres and then propagated to the other brain neuronal networks, as apparent by the patient's clinical features or EEG presentations [2]. The major subtypes of generalized seizures are absence, generalized tonic-clonic (GTC), myoclonic, and atonic.

Absence seizures include staring with loss of responsiveness to external stimuli, sometimes with head nodding or blinking of eyes. Generalized tonic clonic seizures include bilateral symmetrical convulsive movements of both upper and lower limbs with disturbance of consciousness. Myoclonic seizures consist of sudden, brief jerks not associated with disturbed consciousness. Atonic seizures involve a loss of body tone, often resulting in a head drop or fall [1].

Levetiracetam (LEV) is a novel and broad-spectrum antiepileptic drug useful in treating tonic-clonic, partial, and myoclonic seizures and was approved by the FDA in 2000. It modulates voltage-gated calcium channels in the central nervous system. With high pharmacokinetic properties, LEV has an efficient therapeutic effect for the treatment of several types of epilepsy. It is more preferable than older AEDs in the treatment of all types of generalized seizures because it has a more favourable side effect profile in comparison to older AEDs [12] [13] [14] [15].

LEV is effective in the treatment of idiopathic generalized epilepsy [21] [16]. It has complete and rapid absorption after oral administration, with peak plasma concentration about one hour after oral intake, and does not depend on the liver cytochrome P450 enzyme system for its metabolism [17]. LEV is mainly excreted through the kidneys; its plasma half-life is about 7 ± 1 hours in adults, so impairment of renal function causes a decrease in its excretion rate and requires adjustment of its dosage [22].

- If creatinine clearance is between 30 and 50 (mL/min/1.73 m2),
- The recommended dose is 250-750 mg every 12 hours.
- If creatinine clearance< 30 (mL/min/1.73m2)
- The recommended dose is 250-500 mg every 12 hours.
- For patients who are on renal dialysis, 500-1,000 mg every 24 hours.

After dialysis, a 250- to 500-mg added dose is necessary [17]. The most common side effects of LEV on the central nervous system (CNS) include fatigue, sedation, headache, irritability, agitation, depression, confusion, paresthesia, disturbance in memory, slowness in cognition, and, in rare instances, increased suicidal ideation. These are mild side effects; the most dangerous side effects include hallucinations, psychosis, and suicidal thoughts. Since LEV can cause CNS depression and sedation, prescribing it with enzyme-inducing antiepileptic drugs (e.g., carbamazepine and phenytoin) will increase the clearance rate of levetiracetam by 9–22%. Prescribing enzyme-inhibitor drugs like sodium valproate decreased the clearance rate of LEV by 18.8%. Before starting LEV tablets, checking serum creatinine at baseline is required. Routine therapeutic monitoring of LEV is not mandatory; it is generally well-tolerated and there are few cases of overdosages with LEV tablets in the clinical trials. İn addition, there is no antidote for LEV [17].

Nowadays, the most appropriate methods are AI and machine learning techniques, which could be good tools for eploring these medical sections to perform diagnosis and choose the ideal drugs for the patients, and could reduce the workload of clinical experts. Several

researchers used machine learning methods for health problems classifications [24][25][39][40]. ML algorithms are more adaptable techniques that automatically focus on prediction models and learn from given data [26].

Researchers have developed a number of machine learning techniques to predict pharmacological side effects based on different drug properties. Numerous studies have recently documented the use of machine learning algorithms in various medical domains, including cancer genomics [27]. Behnoush et al.'s main objective is applying machine learning to patients who are at high risk of seizures due to tramadol overdose, and they predicted that algorithms could be more precise [28]. Wu et al. [29] created a model by utilizing AI to predict response to antiseizure drugs, suggesting their produced platform could be useful in determining the most important criteria in predicting seizures [30]. Galeano et al. [31] used pharmaceutical graph networks to teach their system globally and to optimize self-representation for medications and drug side effects prediction with a limited number found in randomized controlled clinical trials. Additionally, it has demonstrated that a data integration approach may be used to enhance the capacity of side effect prediction algorithms to detect unidentified adverse effects of drugs that might not manifest even after they are introduced to the market [32].

Evaluating drug side effects is referred to as multi-label prediction challenge, as the drug might have more than one adverse effect. Hatmal et al. [33] used RF, K-star, XGBoost, and MLP for the determination of COVID-19 vaccine's adverse effects. Güneş et al. [34] used SVM, KNN, and MLP for the prediction of the adverse effects of antidepressant medications using random forest and a subsequent reduction optimization technique. Additionally, Huang et al. [36] applied the SVM approach for evaluating anti-cancer medications according to the characteristics of cancer cells. Liang et al. [37] obtained biological pathway characteristics and drug chemical structures as inputs for their technique to predict their pharmacological side effects. Monitoring the patient's body temperature and pulse rate is the primary function of the system [38].

While the application of machine learning models for prediction of drug side effects, including levetiracetam tablets, has not been studied yet in Kurdistan Region in particular, in patients from Erbil Hospital. Thus, one of the main objectives of this study is to develop a system by using machine learning models to assist doctors in making clinical decisions about the possibility of LEV side effects, such as headache, dizziness, and nervousness in patients based on their medical history and symptoms. Moreover, initiation of an appropriate treatment schedule as early as possible saves the patient's life and helps physicians to predict its side effects.

2. Methods

2.1 Data Collection

During 2018-2024, in the outpatient clinic of Erbil Hospital, 200 samples from epileptic patients were collected manually by doctors and their features were age, sex, the first incidence of epilepsy, EEG for determination of epilepsy type (for this research all cases are generalized), brain images, neurological complaint, CBC, LVT, RFT, history of antiepileptic medication, LEV treatment, dosage, duration, whether LEV controlled epilepsy or not, side effects of LEV and follow up every 3 months by CBC, LVT, RFT in addition to the effect of LEV tablets in managing generalized epilepsies.

2.2 Data Preparation

The data has no missing values and is labelled by using label encoding. The standard requirement for many machine learning models is standardization of the dataset, for this purpose, the StanderdScaler technique was used, which implements normalization of the Z-score standardizes attributes to give a distribution with zero mean and unit variance by subtracting their mean from each value and dividing the result by the attribute's standard deviation according to the bellow equation (1):

$$x_i' = \frac{xi-\bar{x}}{s} \quad (1)$$

where mean of the x variable is $\bar{x}$, and xi value is transformed (scaled) x_i' by means from the equation [18].

2.3 Feature Selection

To improve the performance and avoid overfitting, SelectKBest learning was utilized to determine the top relevant features from a larger set of features in the dataset. The authors employed this technique in machine learning to reduce the feature count. The technique used two parameters: the K and A scoring functions. The score function was used to evaluate the important features, and different types of score functions. Chi-square was used to reveal the statistical differences between each feature and the target variables. The numerical value is K, which represents the top number of features to be picked in this work: K = 10.

2.4 Classification

After preprocessing, the data is considered for an input classification process. The algorithms used in our multiclass classification were logistic regression, decision trees, and support vector machines (SVM). In this study, K-fold cross validation technique was used when k was equal to 5. This method is commonly employed in machine learning research. It has provided a more accurate estimate of model performance than traditional testing and training techniques. SVM has been shown to be a powerful classifier in terms of accuracy, precision, recall, and F1_Score.

For evaluation of the data in the present work, these metrics were used: precision, recall, F1_score and accuracy, by using the Eq. (2)(3)(4)(5).

Precision = TP / (TP + FP) (2)

Recall = TP / (TP + FN) (3)

F1-Score = 2 × (precision × recall) / (precision + recall) (4)

Accuracy = (TP + TN) / (TP+TN+FP+FN) (5)

The number of true negative cases is indicated as TN and the number of false positive cases indicated as FP a, while the number of false positive cases is indicated as FP, and the number of true positive cases is indicated as TP [19].

3. Results

As mentioned above, sixty percent of the 200 epileptic patients were female, and forty percent were male. The age range was 11–50 years old, and the male to female ratio was 2:3. The study included generalized epilepsies, 10% of which had a positive family history of the condition, no neurological symptoms at evaluation, no other neurological complaints, and all of which had normal brain MRI results.

The duration of epilepsy in male patients from the age group 1-4 years was 96.34%, and from the age group 5-8 years was 2.44%, while in female patients from the age group 1-4 years was 91.52% and from the age group 5-8 years was 7.62%.

Among 200 cases, 82 of them were on CBZ tablets, 36 cases were on Depakine tablets, 56 cases were on combinations of CBZ and Depakine tablets, and 24 of them were on Levetiracetam tablets (Table 1).

Table 1: Percentage of old treatment type and dose.

Drug type	Dose	Male & Female (%)
Carbamazepine	200mg twice daily 400mg twice daily 600mg twice daily	58.54 31.7 9.76
Depakine	500mg twice daily 1000mg twice daily	94.44 5.56
Carbamazepine and Depakine	200mg twice daily +500mg twice daily 400mg twice daily +500mg twice daily 400mg twice daily +500mg once daily	30.36 53.57 10.07

However, a couple of cases were dealing on LEV tablets 500 mg once daily and twenty-two cases were on no treatment. About 92.5% of the cases that were on this treatment were uncontrolled while 7.5% of the cases were controlled. Among 200 cases, 36 cases were on Depakine tablets, of which 15 cases were controlled, but because of elevated liver enzymes, their treatment was changed to LEV tablets with a lower liver enzymes elevation level.

The starting dose of the LEV tablet was 500 mg twice a day. The dosage was then increased by physicians to 500 mg/dose every 2 weeks until the patient's condition have stabilized with a maximum LEV dosage of 1,500 mg twice daily. Patients of six-month treatment, free from seizure, were continued on this treatment for another six months. About 37.5% of the patients were free of seizures at six months, 50% at one year, and 12.5% at two years were seizure-free.

All of the patients were treated by levetiracetam monotherapy for 2 to 4 years. Their treatment was changed to levetiracetam 500 mg twice a day as a starting dose with gradual tapering of the old treatment; however, the patients dealing with 500 mg and 1000 mg Depakine tablets twice a day were changed to 1000 mg LEV tablets twice a day. All cases were followed up by liver function test, complete blood picture every 3 months, and follow-up EEG after one year.

All of the analysis was conducted on an Intel Core i5 with 8 GB of RAM system and installed Windows 11 version 23H2. Anaconda with Python language version 3.12.4 was used for the experimentation and analysis of the results. The entire process of execution was in Jupiter notebook version 7.0.8, used by Anaconda. Using Pandas for data analysis with the Scikit-learn library was powerful, as Python is used for machine learning tasks.

The present model truly classified patients with side effects to LEV with an accuracy of 0.935. Overall, the results suggested the better performance of our classification model in making initial determinations of the side effects of the LEV drug compared to the physicians' prescriptions. SVM obtained good results in terms of precision, recall, F1_score, and accuracy with values of 0.874, 0.935, 0.903, and 0.935, respectively, compared to two other models' logistic regression and decision tree with values of 0.874, 0.930, 0.901, and 0.930, 0.885, 0.890, 0.890, and 0.885, respectively (Figure 2).

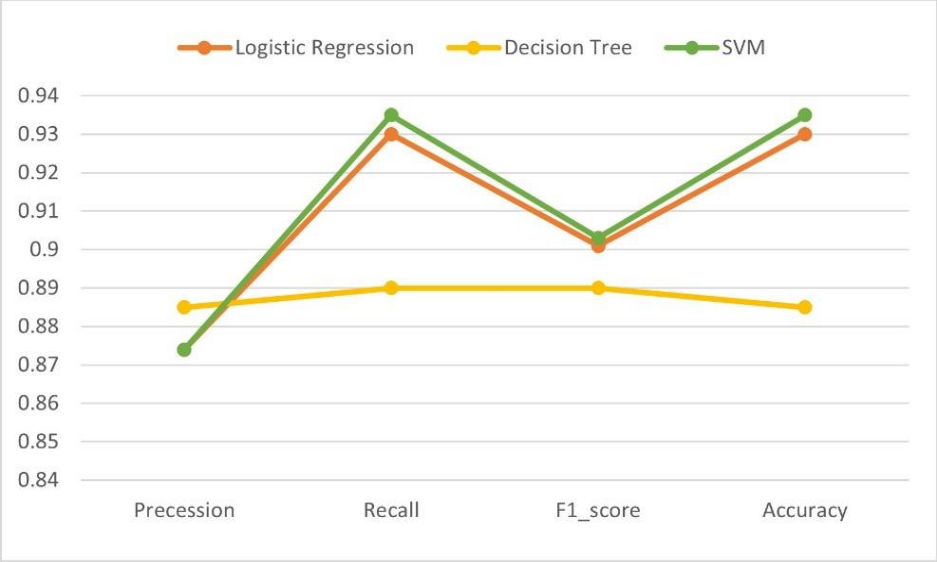

Figure 2: Results of logistic regression, decision tree, and SVM in terms of (precision, recall, F1_score, and accuracy)

4. Discussion

Levetiracetam is a broad-spectrum AED recommended as a first-line therapy in generalised seizure types, including generalised tonic-clonic (GTC), absence seizures, myoclonic, and atonic seizures [20]. Previous studies have proven the efficacy and safety of LEV tablets in relation to several types of epilepsy treatment, and it is more preferable than older AEDs for the treatment of all types of generalised seizures because it has a more favourable side effect profile compared to older AEDs [13] [14] [15].

In evaluating 200 patients with generalised seizures, the authors found that levetiracetam 500–1500 mg twice a day controlled their seizures in a shorter time with fewer side effects and a lower rate of recurrence compared to sodium valproate and CBZ tablets.
After evaluation of the cases, the authors found that the side effects of levetiracetam are lower and milder than those of sodium valproate and CBZ tablets; there were headaches in 3%, dizziness in 2%, and nervousness in 1.5% of cases. Compared to sodium valproate and CBZ tablets, dizziness in 7.5%, vertigo in 1.5%, elevated liver enzymes in 3.5%, and increased weight in 3% of cases were observed upon treatment with sodium valproate.

The machine learning model was able to correctly classify the accuracy of 0.935 and F1_Score 0.903 of patients who actually had side effects (no side effect, headache, dizziness, and nervousness) of LEV by SVM. This study provided a base for designing a system for supporting physicians in making clinical decisions and to help them in identifying side effects of LEV for treating patients with generalised epilepsy more accurately and in a shorter time than the usual required.

Overall, the comparisons made between model predictions and initial physician diagnoses based on patient data highlight the considerable variability that is used for such a decision support system, which may lead to correct treatment or decisions not to use this drug. The authors believed that this model could identify side effects of this drug, reduce the risks to the patient's life before using the drug, and be a useful tool for the doctor to make decisions about the use of the drug.

The limitations of this work were the process of actual data collection, small sample size, and data collection cost, because data was collected manually since no computerized data was available in our country. An increase in the available data can make the study's conclusions more accurate. Also, a lack of prior research studies on our topic.

5. Conclusion

In this study, found that the early diagnosis of epilepsy and the use of proper treatment at the early stages of diagnosis will give better results and will control most seizures in a shorter period of time. A low dose of LEV tablet could achieve the desired therapeutic effect in controlling the generalised epilepsies if started at an early stage of the disease, and it has a higher response rate with less frequency of recurrence. Learning machine models are proper methods for identifying the side effects of the drugs and their risks to patients' lives. This work is a good help for physicians and also for patients for a healthier life.

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