Research Article

Levetiracetam as a Potent and Safe Antiepileptic Drug

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Abstract

A group of new antiepileptic drugs (AEDs) has been clinically established and used. Most of these drugs have new mechanisms of actions that differ from older drugs. Levetiracetam (LEV), a second generation AEDs, is a pyrrolidine derivate compound. The mechanism of action of LEV is different from older AEDs since, it reduces the epileptic seizures through binding to the synaptic vesicle protein 2A (SV2A) receptor. Some studies have reported that LEV, as monotherapy for patients with focal and generalized seizures and safer than AEDs. Other studies concluded that LEV can be used as add-on therapy (Any therapy that is given in addition to the primary or initial therapy to maximize its effectiveness) for patients with focal, myoclonic, and generalized tonic clonic seizures (GTCS). Its pharmacokinetic profile is favorable. It has less drug interaction with other AEDs. This article summarizes the clinical data of LEV in the management of different kinds of epilepsy.

Keywords: Levetiracetam, Epilepsy, Efficacy, Safety, Monotherapy, Add-on therapy.

Introduction

Epilepsy is considered one of the prevalent neurological disorders that affect both children and Adults. At least 50 million people are suffering from epilepsy. The WHO estimates that 4 persons/ 1000 worldwide have a diagnosis of epilepsy[1]. Epilepsy is described by frequent seizures due to abnormal neuronal discharges in the brain[2]. It is categorized according to the kind of seizures into focal and generalized epilepsies[3].

Antiepileptic drugs are the backbone of epilepsy management for patients of all ages. The aim of treating epileptic patients is to completely control seizures without causing unwanted side effects[4]. The selection of AEDs depend on the classification of seizure type, epilepsy syndrome, other medications, comorbidities and lifestyle[5,6,7].

Antiepileptic drugs are classified into three generations. First-generation drugs like Phenytoin (PHT), Phenobarbital (PB), Carbamazepine (CBZ) and Valproic acid (VPA). Second-generation drugs are gabapentin (GBP), Topiramate (TPM), Lamotrigine (LTG), LEV, Rufinamide (RFN) ,Vigabatrin (VGB), Oxcarbazepine (OXC) and Zonisamide (ZNS). The third generation drugs are Lacosamide (LCM), Eslicarbazepine acetate and Retigabine (RTG)[8].

The drugs of first generation of AEDs are mainly given but they cause side effects and require therapeutic drug monitoring (TDM). Therefore, the second generation of AEDs is chosen due to their higher efficacy and safety and less opportunity of interactions with other AEDs[9]. Levetiracetam is considered as a broad-spectrum AED, which also has shown efficacy as monotherapy in drug naive- patients. The aim and objectives of this article to review the clinical response to LEV in treating various types of epilepsy as monotherapy or add-on therapy, pharmacological action, adverse drug reactions and effects of cognitive functions, through literature searches to identify the relevant studies to LEV.

History of Levetiracetam

Levetiracetam is a second generation AED with a chemical structure which is not related to other AEDs. It has a broad-spectrum anti-

epileptic effect that was permitted by the Food and Drug Administration (FDA) in 1999 and can be used as add-on therapy in adults and children patients with focal seizures. It is also used for adults and children patients associated with myoclonic seizures and GTCS[10].

In Europe, this drug was used as monotherapy for treatment of focal seizures in children and adult patients[11]. It was found that LEV has compatible pharmacokinetic parameters, it sparingly suffers from plasma protein binding, lacks hepatic metabolism and can be given twice daily. It has been established to be efficient in the prevention of postoperative seizures associated with patients undergoing neurosurgery operations[12].

Levetiracetam has a wide safety profile compared to other AEDs, it doesn't need therapeutic drug monitoring, and it has no drug interaction with other AEDs. LEV is the drug of choice for epileptic patients due to its favorable pharmacological profile and can be administered as monotherapy or add-on therapy [13].

Chemistry of Levetiracetam

Chemical structure of LEV is not related to other AEDs. It is a derivative of pyrrolidine compound and has a molecular formula of $C_8H_{14}N_2O_2$ **Figure (1)**: LEV is physically characterized by white powder, better taste and has a good solubility in water[14].

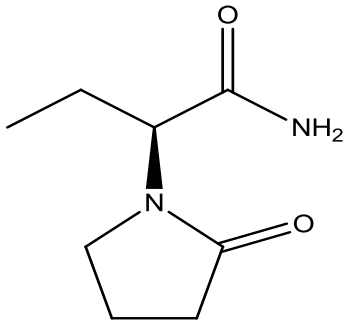

Figure (1): Chemical structure of Levetiracetam [14]

Pharmacodynamic Properties of Levetiracetam

Levetiracetam is structurally not related to other AEDs. The mode of action of LEV is different from the classical AEDs[15].

Levetiracetam has the following effects

(1) Decreasing the epileptic seizures through binding to the synaptic vesicle protein 2A (SV2A), which controls the release of neurotransmitters and excitatory amino acids[16].

(2) Decreasing the release of calcium from intraneuronal vesicles, which leads to changes in the levels of calcium[17,18].

(3) Partially blocking N-type calcium channels, this also leads to changes in the levels of intraneuronal calcium[19,20].

(4) Decreasing some negative allosteric modulators such as zinc, B-carbolines, and γ-aminobutyric acid (GABA) However, LEV does not exhibit the activity of GABA [21].

Pharmacokinetics Properties of Levetiracetam

Levetiracetam is absorbed orally. It has bioavailability higher than 95%, following oral administration, the half-life of LEV in adults is 7 hours, and it can be affected by food[22]. There was a direct correlation between doses of LEV and serum level. Less than 10% of LEV is directly bound to plasma protein. Metabolism of LEV is not dependent mainly on the liver and it does not inhibit or induce the liver enzymes (cytP450)[23].

Levetiracetam is mainly eliminated through the kidney. A bout 65% of LEV is excreted in the urine and 25% of it is metabolized into inactive metabolite and excreted unchanged in the urine. The half-life can be increased to 10-11 hours due to decreasing the renal function in the elderly patients. However the dose of LEV is adjusted in patients with renal failure[24].

Clinical Indications

European Medicines Agency (EMA) and FDA approved LEV to be used as:-

(1) Add on therapy or monotherapy in adult and children patients with focal seizures with or without secondary generalization[25].

(2) Add on therapy or monotherapy in adult and adolescents patients with myoclonic seizures and juvenile myoclonic epilepsy[26].

(3) Add on therapy or monotherapy in adult and children patients with GTCS with or without idiopathic generalized epilepsy[27].

Efficacy and Tolerability

Clinical studies found that LEV was efficient when used as monotherapy in patients with focal and generalized seizures. Some studies concluded improved therapeutic effects of LEV when given as monotherapy in children patients exaggerated with refractory epilepsy **Table (1):**. Alsaadi and coworkers reported that the patients who have been treated with LEV as monotherapy became seizure free after six months and one year of treatment [28].

Lambrechts and his colleagues studied the reduction of seizure frequency in adult patients with focal seizures on using LEV as add on therapy and, were followed-up for 16 weeks of treatment. They found the percentage of reduction in ≥ 50% of seizure frequency was 56.6% of patients and 19.3% of patients became seizure free. This study reported that LEV was efficacious when given as add on therapy in patients with focal seizures[29].

Rosenfeld and coworkers found that patients who have GTCS and treated with LEV had higher response rate than placebo (61.9% vs 29.6%; p = 0.024)[30]. Piña-Garza and coworkers reported that LEV was effective in children patients when used as add-on therapy. They noted that the responder rate was higher in LEV group (43.1%) and then placebo group (19.6%) [31].

Lee and his colleagues found that the percentage reduction in ≥ 50% of seizure frequency was 48% in patients treated with LEV and 22% of patients became seizure free[32].

Swaroop and coworkers compared the efficacy of LEV and CBZ as monotherapy in patients with focal seizures. Efficacy was determined by monitoring the frequency of seizures for three months of treatment. They found both groups had equal percentage of seizure freedom 85.72% after 4th week of treatment, and reported that patients who were treated with LEV had higher percentage of seizure freedom 93.34% compared to CBZ group 89.29% after 12 weeks of treatment [33].

Levetiracetam as add-on therapy in patients with focal epilepsy

Shorvon and his colleagues designed a research to analyze the efficacy and tolerability of LEV when given in a doses 500mg or 1000mg twice-daily after 4 or 12 weeks, they found that the responder rate was significantly higher with LEV treatment (31.6%) than placebo group (10.4%), $p<0.001$[34]. Furthermore Gurses and coworkers studied the frequency of seizures in epileptic patients treated with LEV as add on therapy; they observed the responder rate was higher in patients treated with LEV (60%)[35].

Ben-Menachem E and Falter noted that LEV was effective when used as add-on when given in a dose 3000mg daily to placebo. They found that the responder rate was significantly higher with LEV treatment (42.1%) than placebo group (16.7%), $p<0.001$ [36].

Another study compared LEV when administrated as a monotherapy and given in a dose 2000mg daily to placebo. They reported that the rate of response was higher in patients who were treated with LEV than placebo [37].

Table (1): Studies on the efficacy of levetiracetam in patients with epilepsy.

Study	Design	Patients	Doses	Key findings
Morrell, M.J., et al., 2003	Open labeled community based	1030 adult patients with partial onset seizures	1000 and 3000 mg daily	20% patients were seizure free.
Brodie, M.J., et al., 2007	Monotherapy comparative trial versus controlled relea CBZ	Newly onset focal epilepsy in adults	1000-3000mg LEV daily 400 mg–1200 mg CBZ daily.	73% seizure-free with LEV at 6 months. 72.8% seizure-free with CBZ at 6 months.
Werhahn, K.J., et al., 2015	Monotherapy comparative against LTG and control-release CBZ	Newly onset focal epilepsies in elderly patients aged 60 years or older	1000 mg LEV Daily 100 mg LTG daily 400 mg CBZ daily.	Retention rate after 58 weeks LEV 61.5% LTG 55.6% CBZ 45.8% (p = 0.02).
Berkovic, S.F., et al., 2007	Multicenter, randomized, parallel-group, double-blind, Placebo-controlled.	164 adult with idiopathic generalized epilepsy with generalized tonic-clonic seizures	3000 mg LEV daily	Mean weekly reduction of seizures 56.5% with LEV and 28.2% with placebo (p = 0.004). Responder rates: 72.2% with LEV *versus* 45.2% with placebo(p < 0.001). Seizure freed 34.2% with LEV and 10.7% with placebo (p<0.001).
Wieshmann, U. and G. Baker. 2016	Prospective	329 adult patients with partial or generalized epilepsy	1500 mg LEV daily 225 mg LTG daily 800 mg CBZ daily 1000 mg VPA daily	94% seizure free for LEV 67% seizure free for CBZ. 89% seizure free for VPA. 65% seizure free for LTG.
Sala-Padró, J. et al., 2016	Retrospective	58 adult patients with Juvenile Myoclonic Epilepsy	500-1500 mg LEV daily 400-1100mg VPA daily	63.6% seizure free for LEV 36.7% seizure free for VPA

Table (1): (continued)

Study	Design	Patients	Doses	Key findings
Alsaadi, T.M., et al.,. 2005	Retrospective	46 adult patients with partial seizures	2000 mg daily	45% seizure free after 6 months, 54% seizure free after one year.
Lambrechts, D.A., et al., 2006	Prospective open-label, multicenter	251 adult patients with partial onset seizures	1000 and 3000 mg daily	Reduction in seizure frequency ≥50% in 56.6% and 19.3 % were seizure free.
Rosenfeld, W.E., et al.,. 2009	Double-blind, placebo-controlled	22 adult patients with generalized tonic-clonic seizures	3000 mg daily	Responder rate 61.9% for LEV versus 29.6%with placebo (p = 0.024). Seizure freed from generalized toniclonic seizures 23.8% with LEV and 11.1% with placebo (p < 0.001).
Piña-Garza, J.E., et al., 2009	Multicenter, randomized double-blind, placebo-controlled trail .	116 children patients with partial onset seizures	40-50 mg/kg/day	Responder rate 43.1% for LEV versus 19.6%with placebo (p = 0.013).
Lee, Y.J., et al., 2010	Retrospective	130 children patients with partial and generalized seizures	20-60 mg/kg/day	22 % patients were seizure free.
Suresh, S.H., et al., 2015	Randomized prospective, comparative monotherapy trail versus CBZ .	60 children patients with partial seizures	1000-3000 mg LEV daily 400-1200 mg CBZ daily	85.72% seizure free after 4 weeks for LEV and CBZ. 93.34% seizure free after 12 weeks for LEV. 89.29% seizure free after 12 weeks for CBZ.
Shorvon, S.D., et al., 2000	Multicenter, randomized, parallel-group, double-blind, placebo-controlled	324 Adults, difficult to- treat focal epilepsy	1000 and 2000 mg daily	Responder rate 22.8% with 1000 mg LEV/day, 31.6% with 2000 mg LEV / day 10.4% with placebo ($p \leqslant$ 0.001 for 2000 mg LEV, p = 0.019 for 1000 mg LEV).
Gürses, C., et al., 2008	Prospective	10 adult patient startle epilepsy	1000 and 3000 mg daily	Responder rate 60% with LEV.
Ben-Menachem and Falter. 2000	Multicenter, randomized, parallel group, double-blind, placebo-controlled optional conversio to monotherapy	286 adults difficult-to-treat epilepsy	3000 mg daily	Responder rate 42.1% for LEV versus 16.7% with placebo (p < 0.001).
Chen, D., H. Bian, and L. Zhang. 2019	Multicenter, randomized, double blind, placebo-controlled	3205 adult and children with refractory pilepsy	1000 and 3000 mg daily	Responder rate 2.68, 95% CI 1.99–3.61for LEV *versus* 2.17, 95% CI 1.93–2.43 with placebo (p < 0.05).

LEV: Levetiracetam, CBZ: Carbamazepine, LTG: Lamotrigine, VPA: Valproic acid
Levetiracetam as monotherapy in patients with focal epilepsy

Morrell and coworkers found that the percentage reduction in ≥50% of seizure frequency was 57.9% of patients treated with LEV as monotherapy, the percentage reduction in ≥75% of seizure frequency was 40.1%, moreover 20% of patients became seizure free [38].

Another study compared LEV to CBZ in adult patients with tonic-clonic seizures. It was found that 73% of patients treated with LEV 1000mg daily (500mg twice-daily) became seizure-free and 72.8% of patients treated with 400mg CBZ (200mg twice-daily) were seizure-free [39].

Wu and coworkers reported that patients with focal epilepsy when treated with LEV as monotherapy in doses 1000–3000 mg/day showed a significant reduction in seizures frequency ($p < 0.001$)[40]. Werhahn KJ and his colleagues compared the efficacy of LEV (1000mg daily) as monotherapy to CBZ (400mg) and LTG (100mg daily) in drug naive epileptic patients. They found a significant reduction in seizure frequency of patients treated with LEV and the responder rate was statistically significantly higher for LEV than CBZ and LTG ($p < 0.001$) [41].

Levetiracetam as monotherapy or add on therapy in patients with generalized epilepsy

Previous studies showed that LEV as a potent in patients with generalized epilepsy, they reported that LEV has higher efficacy in epileptic patients [42].

Berkovic and coworkers compared the efficacy of LEV as add on therapy to placebo in patients with GTCS for 6 months. They found 56.5% of patients treated with LEV have greater percentage reduction in weekly frequency of GTCS and 28.2% for placebo group ($p = 0.004$). The rate of response was significantly higher with LEV group than placebo group (72.2% vs 42.3%; $p < 0.001$) [43].

Another study was designed to compare the efficacy of LEV to CBZ in epileptic patients. They noted that the rate of response was higher in patients treated with LEV group than CBZ group (94 % versus 67 %) [44].

Sala and his colleagues concluded that LEV was effective in patients with myoclonic seizures, they found the patients who treated with LEV as montherapy have higher percentage of absence of seizures than patients receiving VPA ($p<0.01$)[45]

Safety of LEV

Clinical studies reporting pooled data supporting the evidence for a satisfying safety of LEV as monotherapy in patients with focal and generalized epilepsy **Table (2)**. Betts T and coworkers reported that the patients who were treated with LEV have some adverse events such as somnolence, asthenia and headache compared to placebo group[46]. Pohlmann and coworkers compared the safety of LEV and CBZ in newly diagnosed focal epilepsy and reported 76.2% of patients with LEV showed adverse events and 82.5% of patients with CBZ showed adverse events[47].

Ansa and his colleagues studied the safety of LEV as monotherapy compared to VPA; they reported that 54% of patients treated with LEV were free from adverse events while 12 % of patients treated with VPA were seizures free. [48].

Table (2): Studies on the safety of levetiracetam in patients with epilepsy.

Study	Design	Patients	Doses	Key findings
Betts T, et al., 2000	Multicenter, randomized double-blind, placebo controlled trail	119 adult with refractory epilepsy	2000 mg -4000 mg daily	Most frequent adverse events: Somnolence and asthenia.
Pohlmann-Eden, B., et al., 2016	Randomized, unblinded comparative mono-therapy trail versus CBZ-CR	308 elderly patients with new diagnosed epilepsy	1000 - 3000 mg LEV daily 600-1600mg CBZ-CR daily	Incidence of adverse events: 76.2% with LEV and 82.5% with CBZ-CR.
Ansa, S., et al., 2016	Prospective observational comparative monotherapy versus VPA	90 children and adult patients with focal and generalized epilepsy	1000 - 3000 mg LEV daily 1000-2000 mg VPA daily	54% of patients with LEV were free from adverse events and 25% of patients with VPA were free. Most frequent adverse events of LEV: headache, fatigue and dizziness.Most frequent adverse events of VPA: headache, weight gain and alopecia.

LEV: Levetiracetam, CBZ: Carbamazepine, VPA: Valproic ac

Adverse Drug Reactions

Bootsma and coworkers found that he most frequent adverse reactions were mood disorder and sleepiness in 5% of patients treated with LEV [49]. Another research was planned to study the effect of LEV on weight of epileptic patients compared to valproate, they found no significant changes in weight [50].

According to Lyseng who found that psycho-logical and behavioral adverse reactions were prevalent in patients treated with LEV[51]. Some studies reported minor changes in certain labo-ratory parameters, such as platelet, white blood cell and neutrophil lymphocyte in patients treated with LEV[52].

Clinical trials reported that LEV was not associated with hypersensitivity reactions, and does not clinically affects hypertensive patients, cardiac patients, laboratory parameters and physical and neurological examinations[53].

Dosage Recommendations

Levetiracetam can be given in a dose 1 gram for adult patients when used as an adjunct therapy; it may be increased to 2g daily. LEV can be given in a dose 20 mg/kg daily for children have weigh <50kg. It can be increased to 60 mg/kg/day. LEV can be given in a dose 500mg twice daily used as monotherapy, It may be increased to 1500mg daily after 2 weeks. It may be raised to 3g daily[54].

Effect of Levetiracetam on Cognitive Functions

Previous studies concluded that LEV has been reported to have good efficacy and improve-ment in the neuropsychological (NP) functions

Table (3)[55,56]. Some results indicated that LEV has good effect on mood and cognition when used as add-on therapy in adult and drug-naive epilepsy patients [57].

Wu and his colleagues reported that improvement in the measured cognitive func-tions in patients with partial epilepsy when treated with LEV as add on therapy [58].

Table (3): Studies on the cognitive functions of levetiracetam in patients with epilepsy.

Study	Design	Patients	Doses	Key findings
Meador, K.J., et al., 2007	Randomized double-blind, two-period crossover	49 adult patients with diagnosed epilep	2000mg LEV daily	Significant improvement in cognitive functions was seen with LEV as monotherapy.
Helmstaedter, C., et al., 2008	Open labeled controlled	288 adult patients and 43 patients on usual medications	1000-3000mg LEV daily	Reports of improved psychomotor speed, concentration and remote memory
Schoenberg, M.R., et al., 2017	Randomized double-blind, placebo controlled crossover	20 healthy adult volunteers	1000mg LEV daily	Patients taking LEV rated their cognitive status as improved and showed improvement on attention and memory tasks.
Wu, T., et al., 2018	Multicenter, randomized, paralleled, double-blind.	58 adult patient partial epilepsy	1000-3000 mg LEV daily	Improved cognition accorc to quality of life measure.
Koo, D.L., et al., 2013	Prospective	55 adult patients with new diagnosed epilepsy	1000-3000mg LEV daily	Significant improvement in verbal fluency, attention, sychomotor speed and executive functions were seen with LEV as monotherapy.
Gomer, B., et al., 2007	Unblended observational – comparing LEV versus TPM	52 adult patients with partial epilepsy	1000-4000mg LEV daily 50-400mg TPM daily	No cognitive adverse effects on tests of cognitive speed, verbal fluency and short term memory with LEV, but difference for TPM
López- Góngora, M., et al., 2008	Prospective	32 adult patients with epilepsy	1000-2000mg LEV daily	Evidence of improvement in working memory, verbal fluency, motor functioning, attention and prospective memory.
Roesche, J., et al., 2004	Retrospective, comparative study versus TPM	39 adult patients with refractory epilepsy	1000-3000 LEV daily	Minor improvement in cognition for LEV but not TPM. Improved digit span and fluid intelligence scores.
Ciesielski, et al., 2006	Open prospective compa-rative trail add on PGB	20 adult patients with treatment resistant partial epilepsy	1000mg LEV daily 300mg PGB daily	Trend for improvement in visual short term memory, attention and executive functions tasks for LEV.
Khanna S, et al., 2019	Prospective, observational, comparative study with VP	60 children patients with epilepsy	500-2000mg LEV daily 300-1000mg VPA daily	Patients on LEV showed cognitive improvement, whereas patients on showed a decline in cognitive functions scores.

LEV: Levetiracetam, TPM: Topiramate, VPA: Valproic acid, PGB: Pregabalin

Dae Lim Koo and coworkers reported improvement in cognitive domains such as psychomotor speed, attention and executive function of patients who treated with LEV as monotherapy[59].

Animal studies reported that rats treated with LEV have a good effect on cognitive measures and improvement in memory functions. These results recommended that LEV may increases learning and memory abilities [60]. Gomer and coworkers studied the effects of LEV on cognitive functions compared to TPM; they concluded that good cognitive measures such as trail making tests A and B of patients with focal seizures and treated with LEV, and impaired cognitive functions of TPM group [61]. Another study established that using LEV as monotherapy in patients with epilepsy was associated with improvement in the measured cognitive functions such as memory and attention [62].

Previous studies reported that patients with partial seizures who treated with LEV have improvement in cognitive functions. These include visual short-term memory, psychomotor speed, concentration and intelligence [63, 64].

Recently, Khanna and coworkers reported the cognitive impairment with the use of valproate in many parameters of cognition that were analyzed. Whereas, improvement in cognition was seen with the levetiracetam on the same parameters [65].

Conclusion

On the light of the current review, it can be concluded that LEV is a second generation antiepileptic drug and can be used as monotherapy or add- on therapy for children and adult patients with focal, myoclonic, and GTCS, furthermore using of LEV as a monotherapy or add on in patients with epilepsy was more effective in improving cognitive functions

Conflict of interest

The authors declare that there is no conflict of interest.

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