Levetiracetam: An Exploration of Neuropsychiatric Abnormalities

Sherin Thomas[1], Reeja Roy[2], Divya Jyothi S[3], Susheela Rani S[4]
[1,2,3]*Department of Pharmacy Practise, Acharya & BM Reddy College of Pharmacy, Bengaluru, Karnataka*
[4]*Assistant professor, Department of Pharmacy Practise, Acharya & BM Reddy College of Pharmacy, Bengaluru, Karnataka*

***Abstract*—Levetiracetam is a second-generation anti-epileptic drug that has become a preferred treatment option for epilepsy due to its highly favourable pharmacological profile. It was synthesized in the 1980s and gained approval in various countries in the early 2000s. This review provides detailed insight into the mechanism, pharmacokinetic characteristics, dosing, indications and neuropsychiatric abnormalities caused by levetiracetam. A comprehensive literature search was conducted using PubMed, Elsevier, and ScienceDirect databases and the search covered publications available till date.**

Research conducted over the years has shown an increased risk of developing various neuropsychiatric abnormalities associated with levetiracetam use. These side effects may include agitation, aggression, hostility, rage, delirium, psychosis, hallucinations, somnolence, depression, restlessness, and exacerbation of seizures. Many of these effects are dose-dependent and usually resolve upon discontinuation of the drug. Additionally, some studies have explored the potential role of pyridoxine in managing these behavioural effects.

Long-term monitoring during initial treatment is vital for detecting and managing complications. Supplements like magnesium, N-acetylcysteine, melatonin, and omega-3 fatty acids may offer neuroprotective and mood-stabilizing benefits, but further clinical trials are needed to confirm their effectiveness in levetiracetam therapy. Ongoing research on strategies to minimize adverse effects will enhance treatment value and epilepsy management.

***Index Terms*—Levetiracetam; anti-epileptic drug; neuropsychiatric abnormalities; psychiatric and behavioural adverse reactions**

I. INTRODUCTION

Levetiracetam is a second-generation antiepileptic drug approved in various countries since the early 2000s, recognized for its efficacy in controlling seizures [1,2]. Its favourable pharmacological profile, minimal interactions with other drugs, and versatility as both a first-line and adjunctive therapy make it a preferred choice for epilepsy treatment [1,3,4,5]. Originally synthesized in the 1980s as part of research into nootropic compounds, levetiracetam received approval in India in 2005 for partial-onset seizures and was later approved by the FDA in 2012 for infants and children aged 1 month and older. An intravenous formulation was also approved in 2006 for patients over 15 who cannot tolerate oral medication [4,6,7,8]. Despite its effectiveness, levetiracetam has been associated with neuropsychiatric side effects such as agitation, mood swings, and fatigue, which can impact patients' quality of life and treatment adherence [2,9]. Research suggests that these effects may be influenced by genetic predispositions and are often dose-dependent or transient as patients develop tolerance over time [5,9].

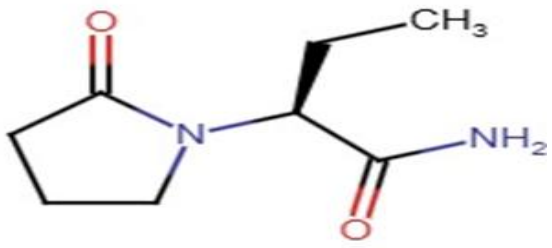

Fig.1 Structure of Levetiracetam

Mechanism of action

Levetiracetam, an antiepileptic drug known for its distinctive mechanism of action involving interaction with the synaptic vesicle protein 2A (SV2A), has shown to be both effective and well-tolerated in the treatment of seizures [5]. Furthermore, it has additional molecular targets that may be combined into a single mechanism of action to account for its antiepileptogenic, anti-inflammatory, neuroprotective, and antioxidant functions. These targets include calcium homeostasis, the GABAergic system, and AMPA receptors, among others [3,6,7,10].

SV2A is a vital membrane protein found in synaptic terminals, playing a key role in managing the readily releasable pool (RRP) and facilitating vesicle priming for neurotransmitter release. During exocytosis, SV2A targets residual calcium, while during endocytosis, it regulates synaptotagmin's vesicle content. After administration, it crosses the blood-brain barrier and binds to SV2A, potentially influencing its function through various mechanisms: it may obstruct SV2A, reducing RRP size and synaptic transmission; stabilize SV2A, enhancing its function; or assist in regulating the expression and trafficking of synaptotagmin in neurons overexpressing SV2A [7]. Levetiracetam also impacts calcium homeostasis, affecting cellular Ca2+ signalling and blocking high-voltage activated Ca2+ channels while hyperpolarizing membrane potential through K+ channel activation [11]. Additionally, it interacts with GABA A receptors to increase GABA levels, reduces glutaminergic excitation by modulating AMPA and NMDA receptors, and enhances glial glutamate transporters [12].

Pharmacokinetic and pharmacodynamic properties

As a member of the pyrrolidone family of nootropic medicines, which has a broad range of action and is regarded as "pharmacologically safe," levetiracetam is a (S)-enantiomer of the ethyl analogue of piracetam, ((S)-α-ethyl-2-oxo-1-pyrrolidine acetamide). This new oral antiepileptic medication has a unique preclinical profile and is structurally different, with a molecular weight of 170.21, compared to current antiepileptic medications [6,8,13-14].

Originating from ethyl acetate it appears as a crystalline powder that ranges from white to off-white. The substance has a subtle odour and a bitter flavour, characterized by the molecular formula C8H14N2O2 [15]. In contrast to numerous other antiepileptic drugs, levetiracetam possesses an extensive therapeutic index, indicating a significant gap between the dosages required to manage seizures and those that result in toxicity. Due to the significant safety margin, serum drug monitoring is not required, except during pregnancy [13].

Absorption: Levetiracetam is rapidly and almost fully absorbed after oral ingestion, with a bioavailability of 96%. Maximum plasma levels occur about one-hour post-ingestion; food can reduce peak concentration by 20% and delay it by 30 minutes but does not affect total absorption. An intravenous (IV) option achieves peak concentration in 5 to 15 minutes, with similar pharmacokinetics to the oral form [4,8,14,16].

Distribution: It binds to proteins at less than 10%, with a plasma half-life of approximately 7 hours [4,8,16]. Steady-state plasma levels are reached after about two days of dosing twice daily. Its volume of distribution in adults is around 0.5–0.7 L/kg, similar to total body water, and it ranges from 0.6 to 0.9 L/kg in infants and children [8,15,16].

Metabolism: Levetiracetam has limited metabolism, with 34% metabolized and 66% excreted unchanged in urine [4,15,16]. Its metabolism does not depend on the liver's cytochrome P450 enzyme system, primarily breaking down through enzymatic hydrolysis of the acetamide group, leading to an inactive metabolite (ucb L057). Other minor metabolites arise from hydroxylation and cleavage of the 2-oxo-pyrrolidine ring [4,16].

Excretion: Most of the drug is excreted unchanged via the kidneys, with a total body clearance of approximately 0.96 ml/min/kg and renal clearance of 0.6 ml/min/kg. About 66% is eliminated in urine without metabolism [4,15,16].

Indications

The antiepileptic drug levetiracetam is accessible in several countries as both liquid and oral formulations, as well as extended-release tablets, providing dosages of 250 mg, 500 mg, 750 mg, and 1000 mg [14,17].

- Myoclonic seizures
- Primary generalized tonic-clonic seizure:
- Partial seizures

Dosing in Paediatrics

For paediatric patients, the recommended oral dosage ranges from 1 gram per day (administered as 500 mg twice daily in immediate-release formulations) to 3 grams per day (administered as 1.5 grams twice daily) [18].

Dosing in Adults

For adults, the initial dosing starts at 1 gram per day (500 mg taken twice daily in immediate-release formulations) and can be increased to the recommended dose of 3 grams per day (1.5 grams taken twice daily) [18].

Levetiracetam is also used off-label for indications that are not approved by the FDA, such as status epilepticus and seizure prophylaxis in cases of subarachnoid haemorrhage [4,19]. Additionally, the drug is utilized off-label for the prevention of seizures related to traumatic brain injury (TBI) and in supratentorial neurosurgery [4]. It is also used off-label to manage seizures in palliative care [10].

II. DISCUSSION

Levetiracetam is one of the most widely used antiseizure drug worldwide [20]. While the drug is generally well tolerated, neuropsychiatric adverse effects may develop after the initial titration period and could be the primary reason for drug withdrawal and treatment failure [1-2,20,21,22,23].

According to research, various risk factors have a role in the development of neuropsychiatric adverse effects. These include a history of psychiatric conditions, previous febrile convulsions, poor seizure control, mental retardation, organic psychosyndrome, impulsive behaviours, and familial predisposition [2,20,24,25,26,27].

Psychiatric manifestations of levetiracetam

Multiple studies have indicated that levetiracetam may have negative psychotropic effects, such as irritability, aggression, suicidal thoughts, mood disorders, and other psychiatric symptoms in both children and adult patients [17,21-22].

An open-label, non-comparative, multicentre, long-term follow-up study conducted by Delanty et al. indicated that despite a favourable safety profile, levetiracetam resulted in psychiatric side effects in up to 13.3% of adults and 37.6% of paediatric patients. Among these individuals, significant symptoms including depression, agitation, hostility, and psychotic behaviour were reported in 0.7% of patients [2,25].

In 2003, Joyce A. et al. highlighted that the use of levetiracetam may lead to significant psychiatric symptoms. They systematically reviewed the clinical features of these symptoms, emphasizing that levetiracetam could cause psychosis and suicidal thoughts in patients [20].

In a randomized controlled trial conducted by Glauser et al. in 2006, along with cohort studies by Mula et al. (2004) and Lee et al. in 2011, it was observed that patients treated with levetiracetam reported one or more adverse events. These events included suicidality, depression, emotional lability, aggression, agitation, hostility, nervousness, and irritability. Notably, these symptoms gradually subsided upon withdrawal of the medication. In a few cases, psychotropic medications were necessary to manage these adverse effects [28,29,30].

Levetiracetam induced depression

Studies suggest that users of levetiracetam are more likely to develop or experience worsening symptoms of depression [31,32,33]. Similar findings are reported in studies by Wieshman et al., Jafar Mehvari Habibabadi et al. (2022), and Rupa Joshi et al. (2019), all of which show an increased risk of depression in patients with epilepsy who use levetiracetam [34,35,36].

The exact mechanism by which the drug may lead to depression remains unclear. Some evidence indicates that anti-seizure medications may contribute to oxidative stress, which can result in behavioural, mood, and cognitive dysfunctions [35,37].

Behavioural effects of levetiracetam

Behavioural abnormalities of levetiracetam have been frequently reported and include a variety of issues such as aggression and changes in mood states, including depression, agitation, hostility, irritability, and hyperexcitability [18,38].

A case-control study conducted by Guilfoyle et al. in 2017 indicated that levetiracetam is among the antiepileptic drugs with the highest frequency of behavioural adverse effects ($P < .0001$) [39].

A study found that during monotherapy, general behavioural problems were noted in 19% of patients, with irritability occurring in 2.6%. In instances of

adjunctive use, irritability was noted in 4.7% of patients, hyperexcitability in 4.4%, and aggressiveness in 2.7% [39].

Speculation exists that these effects may be linked to levetiracetam's influence on the AMPA receptor [12]. Albeit studies conducted suggest that there is no relation between dosage of levetiracetam and the incidence of adverse behavioural effects [40].

Multiple studies have highlighted behavioural issues associated with levetiracetam in children [2,17,41]. A randomized trial by de la Loge et al. (2010) found increased aggression in children on levetiracetam [42]. Piña-Garza et al. (2009) reported somnolence and irritability in very young children [43]. A review by Hansel et al. (2018) showed that children and adolescents experienced more psychiatric and behavioural adverse effects compared to adults [11].

Schiemann-Delgado et al. (2012) reported that 45.6% of patients experienced issues such as headaches, irritability, convulsions, abnormal behaviours and aggression [44]. Chung et al. (2007) found that behavioural symptoms led to 40.4% of discontinuations [45]. Wieshmann and Baker (2013) noted that levetiracetam users reported depression and anger, indicating higher self-reported anger compared to other antiepileptic drugs. Symptoms such as apathy, depersonalization, agitation, anxiety, hostility, and depression were observed [46]. Shukla et al. (2016) found 20.2% of patients exhibited disturbances, including irritability and psychosis, leading to treatment changes [47]. Brodtkorb et al. (2003) identified similar behavioural issues [48].

Kang et al. (2013) highlighted common side effects like irritability (24.3%) and noted that factors like seizure frequency, prior antiepileptic drugs, dosage, and dose escalation rate to maximum dose were not associated with the occurrence of these adverse events [49]. In 2023, Strein et al. found 46% of patients experienced adverse effects, primarily agitation, restlessness, delirium and anxiety [12].

Aggression induced by levetiracetam

An interview-based study by Helmstaedter et al. in 2008 found that many patients taking levetiracetam reported behavioural changes, notably aggression, which was the most significant concern. The effects were linked to poorer seizure control, impulsive and aggressive personality traits. In a follow-up study in 2012, they discovered that aggression-related genes involved in the dopaminergic system were associated with aggressive behaviour, and that levetiracetam interfered with these signals, increasing the risk of negative psychiatric effects [26].

Labiner et al. (2009) conducted a randomized controlled trial that found patients on levetiracetam exhibited increased anger and aggression sub-scores. The most common reason for early withdrawal from the study was adverse events like depression and suicidal ideation, which occurred in 18% of participants [50].

Mula et al. (2003) found that 10% of study participants experienced psychiatric and behavioural adverse effects, with aggression reported by 3.5%. A subsequent study in 2015 revealed that 9.8% of respondents considered aggressive behaviour a persistent issue [27,51].

Psychiatric and behavioural adverse reactions

Studies have shown that levetiracetam is associated with significant psychiatric and behavioural abnormalities. Chen et al. (2017) identified that levetiracetam had the highest adverse effect rate among anti-seizure medications, at 22.1%. Additionally, it had elevated rates of intolerance (17.7%), dose reduction (9.4%), and complete cessation of the medication (8.3%) compared to other antiepileptic drugs. Based on a multicentre case-control study that included 922 patients aged 18 years or younger it was found that psychiatric and behavioural adverse effects occurred in 13.8% of these patients. Overall, a history of psychiatric conditions, absence seizures, intractable epilepsy, and frontal lobe epilepsy were significantly associated with the increased rates of psychiatric and behavioural adverse effects [52-53].

Dinkelacker et al. reported a time frame of 3.6 months from the initiation of levetiracetam treatment to the identification of psychiatric and behavioural adverse reactions. Similarly, Mula et al. noted an average delay of 88 days, primarily associated with symptoms such as aggression, agitation, anger, and hostility. However, other studies indicate a much shorter interval of less than one month [11].

A study by Kaiyan Tao et al. found that psychiatric symptoms from levetiracetam typically arise within the first three months, with 38% of patients experiencing symptoms within four weeks. Severe symptoms were often linked to prior psychiatric issues

and included hallucinations and persecutory delusions. Irritability and aggressive behaviour, often triggered by environmental factors, were common, with serious concerns such as suicidal thoughts. Symptoms usually resolved after dosage adjustment or discontinuation, although some patients continued to face significant issues [20].

A study by Sudhir Chandra Sarangi et al. found that patients using levetiracetam experienced more psychiatric and behavioural adverse effects ($p = 0.010$) compared to those on conventional antiepileptics with significant decline in sleep quality, increased physical aggression, and higher levels of anger [5]. Additionally, research by Cramer et al. (2003) and Weintraub et al. (2007) documented incidences of psychosis, altered behaviour, emotional instability, and hostility among patients [9,33].

Levetiracetam induced suicidal behaviour

Previous studies have reported that the incidence of suicidal ideation among epilepsy patients taking levetiracetam is approximately 0.5–0.7% [9,54]. In a case report by Hoo Rim Song et al., a 50-year-old man was prescribed levetiracetam, starting at a dosage of 500 mg per day, which was gradually increased to 1000 mg per day. He initially experienced passive suicidal ideation that later progressed to active suicidal thoughts. However, these suicidal thoughts disappeared within five days after the discontinuation of levetiracetam [55].

Levetiracetam induced mania

Halil Ozcan et al conducted a case report on mania induced by levetiracetam involving a 37-year-old female patient with no history of psychiatric illness, treated for uncontrolled seizures. After starting and increasing the dose of levetiracetam, she developed symptoms like grandiosity, speech disorder, irritability, distractibility, decreased need for sleep, flight of ideas, and persecutory delusions. Upon discontinuation of the medication, her manic and seizure symptoms gradually declined within a week. The study suggested that levetiracetam may have multiple effects on neurons—particularly opposing effects on GABA, glycine-gated currents, and inhibition of N-type calcium channels—that could lead to behavioural disturbances, including manic symptoms [56].

In a 2019 case report by Ali Ercan Altınöz et al, a 52-year-old male with generalized tonic-clonic epilepsy developed a hypomanic episode after his dosage of levetiracetam was increased due to more frequent seizures. He had no prior psychiatric history, but experienced irritability, reduced sleep, increased energy, loud speech, and abusive language within two weeks, leading to a diagnosis of medication-induced bipolar disorder. His condition normalized after discontinuing levetiracetam [57].

Levetiracetam induced psychosis

Among various neuropsychiatric abnormalities, psychosis has been infrequently reported in patients using levetiracetam [25]. The symptoms were always reversed with levetiracetam discontinuation [58].

Approximately 1–1.4 percent of people using levetiracetam are anticipated to develop psychosis [2,22].

Studies conducted by Campbell C et al., Anna Rosati et al. and Florentina M.E. Pinckaers et al. have shown that levetiracetam use can lead to psychotic reactions like vivid hallucinations, misidentifications, delusions, and psychotic thoughts that result in drug discontinuation [17,21,38].

The mechanisms behind the psychotic symptoms induced by levetiracetam are still being researched. Studies have shown that these symptoms are significantly linked to several factors, including status epilepticus, previous history of psychotic symptoms, history of psychiatric conditions other than psychosis, female gender, history of febrile convulsions, and intellectual disabilities [25,38].

A study by Mahmood Motamedi et al. (2003) found that 14.3% of patients discontinued levetiracetam due to a severe delayed psychotic syndrome, characterized by psychotic thoughts, insomnia, and personality changes, occurring 4-9 months after initiation. Symptoms resolved upon discontinuation of the drug [59].

Levetiracetam induced rage and delirium

Levetiracetam-induced rage is a rare neuropsychiatric ADR characterized by intense rage, uncontrollable anger, fits of fury, depression, violence, and suicidal tendencies. This occurs more in patients with a history of mood or psychiatric disorders. A case report by Orakwue A. Molokwu et al. examined two patients taking levetiracetam, both of whom experienced

episodes of seething rage, fits of fury, aggressiveness, and suicidal thoughts, despite a reduction in seizure frequency. Neuropsychiatric symptoms emerged within the first week and intensified by the second week. Withdrawal and reintroduction of the drug led to the cessation and reemergence of these symptoms respectively [24].

While early clinical trials reported some mild neuropsychiatric adverse effects, delirium is rarely linked to levetiracetam use. A case report by Eileen S. Hwang et al. (2014) details a 77-year-old male who developed disorientation, agitation, garbled speech, and lethargy within 24 hours of starting levetiracetam at 500 mg intravenously twice daily for post-traumatic seizures. His symptoms persisted for 12 days despite treatment with sedatives and antipsychotics, and he required restraints due to aggressive behaviour. Discontinuing levetiracetam led to the resolution of his symptoms [60].

Levetiracetam induced hallucination

Another uncommon side effect of levetiracetam is the development of hallucinations. A case report by Seher Erdogan et al. covers a 10-year-old boy who suffered visual and auditory hallucinations while using levetiracetam, which resolved within 48 hours of discontinuing the drug [61].

According to Shakya et al., a 32-year-old patient with refractory epilepsy experienced auditory hallucinations during the third week of levetiracetam treatment. These symptoms disappeared three days after the medication was stopped [62].

Levetiracetam induced cognitive effects

Somnolence, asthenia, and coordination difficulties often occur within the first four weeks of treatment with levetiracetam [18]. In an RCT by J. J. Cereghino et al., CNS-related adverse effects, mainly somnolence, led to patient withdrawals. Other effects included headache, dizziness, and asthenia.

Studies by Shorvon et al. (2000) and Berkovic et al. (2007) reported similar CNS-related effects with an incidence of more than 5% [64-65].

According to a prospective study conducted by Ekaterina I. Viteva et al., 13% of patients had tiredness, disorientation, dizziness, memory impairment, numbness, non-epileptic seizures, melancholy, speech difficulties, and visual hallucinations [66]. Schoenberg et al. (2017) noted that while levetiracetam was well tolerated in healthy older adults, there was a significant increase in irritability [67]. Eylert Brodtkorb et al. (2003) identified cognitive issues like unsteadiness, dizziness, tremors and memory problems [48].

Lee et al. (2011) revealed CNS-related adverse events from levetiracetam, including somnolence, asthenia, memory problems, and extreme stress. Wieshmann and Baker (2017) reported a 54% prevalence of memory problems, difficulty concentrating, and feelings of anger associated with levetiracetam [30,34].

Levetiracetam associated seizure aggravation

Numerous studies have documented an increase in the frequency of seizures or a worsening of seizure episodes in individuals receiving levetiracetam therapy, which resolved when the medication was discontinued [68,69,70,71].

Caraballo et al. (2009) observed behavioural abnormalities, increased seizure frequency, and unstable gait [72]. Anna Szucs et al. found that seizure frequency had increased, with 4% of patients experiencing de novo GTCS [73].

Karl O. Nakken et al. reported that levetiracetam was associated with somnolence in 18% of adults and 7% of children, along with higher seizure rates (18% in adults and 43% in children) [74].

III. CONCLUSION

The studies reviewed vary widely in design, population, diagnostic criteria, and outcome reporting, often being anecdotal or descriptive without robust controlled trials. Neuropsychiatric issues linked to levetiracetam, especially in the early treatment phases, present significant concerns. Long-term monitoring during the initial weeks to months is essential for effectively managing these complications. Fortunately, evidence indicates these effects are typically reversible upon discontinuation. Patients, families, and caregivers should be informed of these potential neuropsychiatric effects to encourage early intervention and treatment adherence. Additionally, supplements like magnesium, N-acetylcysteine (NAC), melatonin, and omega-3 fatty acids show promise for neuroprotection and mood stabilization, but further clinical trials are needed for specific evaluation alongside levetiracetam. Despite its neuropsychiatric profile, when carefully managed,

levetiracetam remains a valuable first-line antiepileptic medication. Continued research into minimizing adverse effects will enhance its therapeutic benefits and improve epilepsy management.

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