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ORIGINAL RESEARCH

Assessing the Incidence Rate of Neuropsychiatric Adverse Effects in Older Adults Following Levetiracetam Initiation: A Retrospective Study

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Background: Levetiracetam (LEV) is commonly prescribed for epilepsy management. However, neuropsychiatric disorders (NPDs) are concerning adverse effects that may result in medication discontinuation. This study aims to examine the incidence and factors influencing LEV associated NPDs in adult patients aged 50 years and above.

Methods: A retrospective analysis was conducted on patients aged 50 years and above prescribed LEV between 2010 and 2020, with at least one follow-up appointment six months post-treatment initiation. The incidence of new-onset or aggravated NPDs and variables potentially influencing this risk were examined. Independent *t*-test, chi-squared, and Fisher's exact test were used, in addition to univariate and multivariate logistic regression.

Results: The study included 100 patients with a mean age at LEV start of 63.31 years (SD = 16.48). Neuropsychiatric symptoms were observed in 6 (6.0%) patients. Factors associated with new-onset NPDs were younger age at epilepsy diagnosis (p=0.005), younger age at LEV start (p=0.004), and concurrent use of Carbamazepine/Oxcarbazepine (p=0.004). On multivariate analysis, only the association with Carbamazepine/Oxcarbazepine remained significant (OR 14.62, 95% CI 1.86–114.70, p=0.011).

Conclusion: The findings indicate that the incidence of NPDs in elderly patients is relatively low (6%). Further research with larger samples is needed in comparison with a younger sample as a control group to confirm these findings.

Keywords: levetiracetam, neuropsychiatric disorders, elderly patients

Introduction

Epilepsy is a common neurological disorder characterized by a sustained propensity to generate epileptic seizures, leading to a spectrum of cognitive, psychological, and social repercussions. It manifests with transient motor (the most frequent), sensory, sensitive, autonomic, or cognitive symptoms originating from abnormal excessive or synchronous neuronal activity within the brain that results from an imbalance between excitation and inhibition of neuronal circuits.[1] According to the WHO, it is estimated that 5 million people are diagnosed with epilepsy every year worldwide, with about 80% of epileptic patients living in low- and middle-income countries.[2] Nonetheless, the availability of effective antiseizure agents considerably reduced the burden of this disorder, as over 70% of the affected individuals can live seizure-free if properly diagnosed and treated.[2]

Levetiracetam (LEV), a pyrrolidone derivative developed from piracetam, is among the first-line medications for epilepsy. It has demonstrated tolerability and effectiveness against both focal and generalized seizures in children and adults.[3,4] The pharmacological effects of LEV are attributed to its modulation of neuronal activity through various mechanisms. It binds to the synaptic vesicle protein 2A (SV2A), a glycoprotein essential for presynaptic neurotransmission present mainly in the cortex, thalamus, basal ganglia, and hippocampus, leading to a decreased seizure threshold in epileptogenic brain areas.[5] Furthermore, LEV has additional potential antiseizure effects. It increases the levels of the inhibitory neurotransmitter GABA and neurosteroids such as allopregnanolone, while decreasing excitatory glutamate. It also modulates serotonergic, α2-adrenergic, and μ-opioid receptor-mediated signaling, and reduces intraneuronal calcium levels.[6,7]

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However, these effects of LEV can result in secondary interference with other neurological functions such as mood and behavior regulation, ultimately leading to neuropsychiatric disorders (NPDs).[6] A case–control study involving 841 patients with a mean age of 44.7 years old showed that LEV therapy was independently associated with greater frequency of anger/aggression, nervousness/agitation, depression, and sleep disturbance, compared to other treatments.[8] In another large case–control study of 4085 epilepsy patients (mean age: 41 years), LEV displayed the highest rates of psychiatric adverse events compared to the other antiseizure medications (ASMs). These effects resulted in higher intolerability rate of 17.7%, a dose reduction rate of 9.8% and complete cessation rate of 8.3%.[3] Moreover, previous systematic reviews of safety revealed that following LEV therapy, the incidence of somnolence was 14.8%, dizziness 8.8%, depression 4%, nervousness 3.9%, insomnia 3.1%, hostility 2.3%, anxiety 1.8% and emotional lability 1.7%.[9,10]

ASMs are commonly prescribed drugs for the elderly population, as they are particularly susceptible to new-onset epilepsy, often symptomatic and a consequence of epilepsy-causing geriatric conditions such as stroke and Alzheimer's disease.[11] Furthermore, aging is a known factor that influences the pharmacokinetics and pharmacodynamics of drugs, which may favor the development of ASMs-related side effects including mental disorders.[12] Another significant concern is that LEV-associated NPDs can range in severity and, in some cases, lead to either discontinuation of LEV or the initiation of psychotropic medications.[13] However, the incidence of LEV-induced NPDs in the elderly population remains insufficiently explored. In response to this gap, we conducted the present research to determine the frequency and factors of these reactions in geriatric patients, aiming to enhance medication safety and adherence for this demographic.

Aim & Objectives

The aim of this study is to evaluate the neuropsychiatric side effects of LEV in an elderly population. This assessment serves to not only quantify the risk of new or exacerbated NPDs associated with LEV use but also to determine potential factors that might influence this risk. The following objectives were explored:

- To estimate the incidence risk of new-onset or aggravated neuropsychiatric adverse effects associated with LEV among older adults.
- To identify potential factors influencing the risk of these adverse effects.
- To assess the efficacy of LEV in managing seizures in older adults.

These findings could contribute to refining prescribing practices, enhancing patient safety and potentially improving the quality of life for older adults dealing with seizure disorders. It could serve to guide physicians in making informed decisions when initiating LEV in this specific population, being fully aware of its potential benefits and drawbacks.

Methods

Study Design and Setting

This study was designed as a retrospective analysis, carried out at the outpatient Department of King AbdulAziz University Hospital (KAUH), Jeddah, Saudi Arabia.

Participants

The study population comprised adults aged 50 years and above who had been prescribed LEV between the years 2010 and 2020. For inclusion in the study, participants had to have at least one follow-up appointment attended six months or more after the initiation of the LEV treatment.

Sampling

We used a random sampling method for this study, which involves selecting individuals from the pool of patients aged 50 years and above, visiting the outpatient clinic department at KAUH. The targeted participants for our sample are individuals aged 50 years and above who have been diagnosed with epilepsy or seizures and either previously prescribed LEV and are still taking it or have started taking LEV after their first visit.

Data Collection

The collection of necessary data elements was undertaken meticulously from the medical records available at King AbdulAziz University Hospital. This data encompassed demographics such as age, gender, and weight, as well as specific medical details. The latter included past medical history, particularly stroke, dementia, and psychiatric disorders, and medication history focusing on the use of ASMs. Further detailed data were collected regarding the pattern of LEV prescription. This involved the age at which treatment commenced, frequency and dosage of LEV, duration of treatment, and presence of any associated ASMs. Data specific to the medication's efficacy, such as the incidence of seizures post-treatment, were also recorded. Finally, we identified and recorded any occurrence of new-onset or aggravated neuropsychiatric adverse effects.

In the interest of protecting patient privacy, all personal identifying information was omitted from the collected data, thus maintaining patient anonymity throughout the study.

Data Analysis

All data, once collected and coded, were analyzed using the Statistical Package for Social Sciences (SPSS) software, version 21 for Windows. Categorical variables were represented in terms of percentages, while the distributions of continuous variables were presented as means and standard deviations. The Independent *t*-test was utilized to compare the means of two independent groups for normally distributed data. The Chi-square test was employed for comparing categorical variables, and Fisher's exact test was utilized when the expected count in any cell of a contingency table was below 5. Additionally, univariate and multivariate logistic regression analyses were conducted to analyze factors associated with new-onset NPDs among the subjects. The univariate logistic regression was performed to explore the relationship between each independent variable and the dependent variable separately, while multivariate logistic regression was applied to identify the independent factors associated with NPDs, adjusting for possible confounders. All tests were two-tailed, and a p-value less than 0.05 was considered statistically significant.

Ethical Clearance

This study was conducted with strict adherence to ethical considerations to ensure the protection and respect of the patients involved. Confidentiality and privacy were prioritized throughout the data collection and analysis process. The patient data utilized in this retrospective study were anonymized and de-identified before use, to protect the patients' identities and sensitive information. The research protocol was reviewed and approved by the Institutional Review Board at King AbdulAziz University Hospital, and it was carried out in accordance with the Declaration of Helsinki and its later amendments or comparable ethical standards. Furthermore, as this study involved a review of past patient records, informed consent was not directly obtained from the patients; however, all data were handled with the utmost care to preserve confidentiality and privacy.

Results

Baseline Characteristics and Outcome

We included 100 patients, 55 of them were male, and the mean age was 63.31 (range 50–97) years. Medical history showed a high prevalence of stroke (60%), while psychiatric history showed dementia (9.0%) and other psychiatric disorders (7.0%), and 10 of the participants were taking psychiatric drugs. New-onset neuropsychiatric symptoms were recorded in 6 (6.0%) patients. No worsening of previously reported psychiatric symptoms was identified in this sample (Table 1). Thus, the incidence of neuropsychiatric adverse effects was estimated as 6% (95% CI: 2.2–12.6%).

Patterns of LEV Prescribing

The majority (98%) received the drug twice daily (BID). The most commonly prescribed LEV dosage was 500 mg (55.0%), followed by 1000 mg (17.0%) per dose. All patients continued the drug for at least six months. The use of associated ASMs

Table 1 Baseline Characteristics and Outcomes

Parameter	**Mean**	**SD**
Age at epilepsy diagnosis, in years	59.68	20.93
Weight (kg)	74.01	16.16
Parameter	**N**	**%**
Gender		
Male	55	55.0
Female	45	45.0
Medical history		
Stroke	60	60.0
Dementia	9	9.0
Psychiatric disorder	7	7.0
Psychiatric drugs	10	0.0
Other antiseizure drugs		
Phenytoin	25	30.0
Valproic acid	10	10.0
Carbamazepine / Oxcarbazepine	15	15.0
Topiramate	6	6.0
Lamotrigine	7	7.0
Others	20	20.0
Outcomes		
New-onset neuropsychiatric symptom	6	6.0

was prevalent, with phenytoin being the most common (25.0%), followed by "Others" category drugs (17.0%) and Carbamazepine/Oxcarbazepine (15.0%). The majority of these drugs were prescribed before the patient was seen in the neurology clinic and then started on LEV. Majority of the patients were prescribed with only one associated ASM (61.0%). Treatment efficacy showed that 38% of the patients became seizure-free, while 19% were partially improved. However, data were missing or patients were lost to follow-up in 34% of the cases. Please refer to Table 2 for a detailed breakdown of the data.

Factors Associated with NPDs

Factors associated with new-onset NPDs among patients on LEV treatment were examined in Table 3. The younger age at diagnosis and LEV start were significantly associated with NPDs, with mean ages at diagnosis being 61.21 years for patients without NPD and 37.00 years for those with NPDs (p=0.005*), and mean ages at LEV start being 64.53 years and 45.00 years, respectively (p=0.004*). Although not statistically significant, the prevalence of NPDs was higher in females (11.1%) than males (1.8%), and in those with a psychiatric disease history (28.6%) compared to those without (4.3%). The use of a maximum dose of 1000 g or higher of LEV was associated with a higher incidence of NPDs (12.5%) compared to those on a lower dose (2.9%), but this difference was not statistically significant. On the other hand, the concurrent use of Carbamazepine/Oxcarbazepine was significantly associated with the occurrence of NPDs (26.7% vs 2.4%, p=0.004*). Additionally, associated Lamotrigine use showed a higher prevalence of new-onset NPDs, with 28.6% among users versus 4.3% among non-users, though this difference was not statistically significant (p=0.055).

Table 2 Patterns of Levetiracetam Prescribing (N=100)

Parameter	**Level**	**Statistics**	
Age at start of LEV (years)	Mean, SD Median, range	63.31 65.5	16.48 4, 92
Parameter	**Level**	**Frequency**	**Percentage**
Frequency	OD BID	2 98	2.0 98.0
Maximum dose (mg) per dose	250 500 750 1000 1500 2000	4 55 9 17 7 8	4.0 55.0 9.0 17.0 7.0 8.0
Drug continued at least 6 months	Yes	100	100.0
Associated ASMs	Phenytoin	25	25.0
	Valproic acid	10	10.0
	Carbamazepine / Oxcarbazepine	15	15.0
	Topiramate	6	6.0
	Lamotrigine	7	7.0
	Lacosamide	3	3.0
	Others	17	17.0
Number of combined antiseizure medications	0 (LEV alone) 1 2 3	28 61 10 1	28.0 61.0 10.0 1.0
Treatment efficacy	Seizure free Partially improved No improvement Deceased No data or lost followup	38 19 4 5 34	38.0 19.0 4.0 5.0 34.0

Abbreviation: LEV, levetiracetam.

Interestingly, no cases of new-onset NPDs were reported among patients who had complete therapeutic response (seizure-free). Please refer to Table 3 for more detailed information.

Predictors of NPDs

Table 4 delineates the independent factors associated with new-onset NPDs. Univariate analysis revealed that the age at diagnosis (Odds Ratio (OR) 0.96, 95% Confidence Interval (CI) 0.93–0.99, p=0.014*) and age at LEV start (OR 0.95, 95% CI 0.92–0.99, p=0.012*) were significantly associated with decreased risk of these disorders. Additionally, the concurrent use of Carbamazepine/Oxcarbazepine increased the risk considerably (OR 15.09, 95% CI 2.47–92.23, p=0.003*). However, upon multivariate adjustment, only the association with Carbamazepine/Oxcarbazepine remained significant (OR 14.62, 95% CI 1.86–114.70, p=0.011*), indicating it as an independent risk factor for new-onset NPDs in patients on LEV. For more detailed data, refer to Table 4.

Table 3 Factors Associated with New-Onset Neuropsychiatric Disorders

Factor	Level	New-Onset or Aggravated NPDs				p-value
		No (n=94)		Yes (n=6)		
		Mean	SD	Mean	SD	
Age at diagnosis	(years)	61.21	19.76	37.00	26.46	0.005*[a]
Age at LEV start	(years)	64.53	15.45	45.00	22.12	0.004*[a]
		N	%	N	%	
Gender	Male Female	54 40	98.2 88.9	1 5	1.8 11.1	0.088
Stroke history	No Yes	39 55	97.5 91.7	1 5	2.5 8.3	0.397
Dementia	No Yes	85 9	93.4 100.0	6 0	6.6 0.0	1.000
Psychiatric disease	No Yes	89 5	95.7 71.4	4 2	4.3 28.6	0.055
Maximum dose	<1000 g ≥1000 g	66 28	97.1 87.5	2 4	2.9 12.5	0.081
Phenytoin	No Yes	64 30	91.4 100.0	6 0	8.6 0.0	0.174
Valproic acid	No Yes	79 15	92.9 100.0	6 0	7.1 0.0	0.587
Carbamazepine / Oxcarbazepine	No Yes	86 8	95.6 80.0	4 2	4.4 20.0	0.109
Topiramate	No Yes	93 1	93.9 100.0	6 0	6.1 0.0	1.000
Lamotrigine	No Yes	93 1	93.9 100.0	6 0	6.1 0	1.000
Others	No Yes	92 2	93.9 100.0	6 0	6.1 0.0	1.000
Associated Phenytoin	No Yes	68 26	91.9 100.0	6 0	8.1 0.0	0.335
Associated Valproic acid	No Yes	84 10	93.3 100.0	6 0	6.7 0.0	1.000
Associated Carbamazepine / Oxcarbazepine	No Yes	83 11	97.6 73.3	2 4	2.4 26.7	0.004*
Associated Topiramate	No Yes	88 6	93.6 100.0	6 0	6.4 0.0	1.000
Associated Lamotrigine	No Yes	89 5	95.7 71.4	4 2	4.3 28.6	0.055
Associated Lacosamide	No Yes	92 2	94.8 66.7	5 1	5.2 33.3	0.171

(*Continued*)

Table 3 (Continued).

Factor	Level	New-Onset or Aggravated NPDs				p-value
		No (n=94)		Yes (n=6)		
		Mean	SD	Mean	SD	
Other associated ASM	No	77	92.8	6	7.2	
	Yes	17	100.0	0	0.0	0.586
No. associated ASMs	0	27	96.4	1	3.6	
	1	58	95.1	3	4.9	
	2	8	80.0	2	20.0	
	3	1	100.0	0	0.0	0.266[b]
Treatment efficacy	Seizure-free	38	100.0	0.0	0.0	
	Partially improved	16	84.2	3	15.8	
	No improvement	2	66.7	1	33.3	
	Deceased	5	100.0	0	0.0	
	Discontinuation	1	100.0	0	0.0	
	Seizure-free on other ASM	1	100.0	0	0.0	
	No data or follow up	31	93.9	2	6.1	0.122[b]

Notes: *Statistically significant result (p<0.05). Test used: [a]independent *t*-test; [b]chi square test; otherwise, Fisher's exact test was used. Noting that complete therapeutic response (seizure-free) was associated with no case of new-onset neuropsychiatric disorder.
Abbreviations: NPDs, neuropsychiatric disorders; ASMs, antiseizure medications.

Table 4 Independent Factors Associated with New-Onset Neuropsychiatric Disorders Among Patients on Levetiracetam

Predictor / Level	Univariate				Multivariate			
	OR	95% CI		p-value	OR	95% CI		p-value
Age at diagnosis (years)	0.96	0.93	0.99	0.014*	1.01	0.94	1.09	0.775
Age at LEV start	0.95	0.92	0.99	0.012*	0.94	0.86	1.04	0.226
Associated Carbamazepine / Oxcarbazepine	15.09	2.47	92.23	0.003*	14.62	1.86	114.70	0.011*

Note: *Statistically significant result (p<0.05).
Abbreviations: OR, Odds ratio; 95% CI, 95% confidence interval.

Discussion

Summary of Findings

This retrospective study of 100 older adult patients examined the neuropsychiatric side effects of LEV in the elderly. The risk of new-onset or aggravated neuropsychiatric adverse effects linked to LEV was estimated at 6.0%. We identified several factors influencing the risk of such adverse effects. Younger age at epilepsy diagnosis and LEV initiation were significantly associated with the onset of NPDs. Additionally, concurrent use of Carbamazepine/Oxcarbazepine was found to be an independent risk factor for the onset of such disorders in patients on LEV, even after adjusting for possible confounders. In terms of LEV's efficacy in managing seizures, 38% of the patients became seizure-free, while 19% were partially improved. However, a significant number of patients were either lost to follow-up or data were missing, making it challenging to draw a definitive conclusion about LEV's efficacy in seizure management.

Incidence Risk of Neuropsychiatric Adverse Effects

In this study, we observed a 6% incidence of LEV-induced NPDs in elderly epileptic patients. While this rate cannot be directly compared to other studies due to a lack of data specific to the geriatric population, it is lower than reported rates in

younger cohorts. For instance, a study by Josephson et al reported a higher NPD incidence, with 14.1% of 1173 adults (median age: 39) manifesting psychiatric symptoms or disorders over a 2-year prescription period. Notably, this study introduced two predictive models for LEV-induced psychiatric adverse events and validated their effectiveness.[14] Another study involving 568 epileptic patients (mean age: 33) found that using LEV, either as monotherapy or in combination, was associated with irritability in 24% of patients, dizziness in 20.1%, headache in 11.8%, somnolence in 11.6%, depression in 6.9%, and psychosis in 1.1% after a 29.3-month follow-up.[15] Such adverse events could significantly influence treatment discontinuation in the elderly, especially as LEV's tolerability is known to decrease with age.[16]

The Influence of Patient Age at Diagnosis and LEV Start on NPDs

We identified a positive correlation of the emergence of NPDs with an earlier diagnosis of epilepsy and LEV initiation. Both factors indicate a prolonged duration of LEV consumption, potentially leading to more pronounced disruptions in neuronal function. It is suggested that repeated LEV administration might exert a cumulative effect on neurons, heightening the risk for psychiatric manifestations.[17] Prolonged inhibition of certain neurotransmissions, such as glutamatergic and serotoninergic, coupled with a chronic increase in GABA activity, might induce sustained alterations in cognition, behavior, and mood regulation. This theory aligns with evidence that LEV's inhibition of synaptic vesicle release is both stimulation- and time-dependent,[18] suggesting deeper neuronal interference after extended use. Additionally, patients with a long epilepsy history are more likely to be exposed to other ASMs that could disrupt CNS neurotransmission. When combined with LEV, these effects might be amplified, increasing the likelihood of NPD development.

The Role of Concurrent Carbamazepine/Oxcarbazepine Use

Co-administration of LEV with the enzyme-inducing antiseizure drug Carbamazepine increases LEV clearance by 24–37%, thereby reducing its retention in the body.[16] Carbamazepine levels remained stable when LEV was introduced to patients with resistant epilepsy.[19] Similarly, Oxcarbazepine's potential to boost LEV retention appears minimal.[20] This indicates that the heightened LEV toxicity when combined with carbamazepine or oxcarbazepine stems from a pharmacodynamic interaction rather than a pharmacokinetic one.[19] ASM-induced psychiatric anomalies are believed to arise from the modulation of neurotransmitters like glutamate (through AMPA receptor inhibition) and serotonin, and the amplification of GABA-dependent signals, all of which influence behavior and mood regulation.[6] Given that LEV, carbamazepine, and oxcarbazepine all interact with these neurotransmitters in the CNS, their combined use could intensify mood and behavioral changes.[6,21–23]

Efficacy of LEV in Managing Seizures

LEV is a primary treatment option for epilepsy and is particularly effective in elderly patients.[24] Besides its clinical safety and effectiveness,[3,4] fundamental research has shown that LEV has several mechanisms of action, such as binding to synaptic vesicle protein 2A (SV2A), enhancing inhibitory neurotransmitters like GABA, restoring brain levels of allopregnanolone, and reducing and modulating various excitatory and pro-epileptic neurotransmitters.[5–7] The American Academy of Neurology and the American Epilepsy Society advocates for LEV in managing adults with new-onset epilepsy, based on its proven efficacy in clinical trials.[25] In Phase III clinical trials, LEV, as an add-on therapy at doses between 1000 and 3000 mg/day, reduced seizure frequency in patients with partial-onset seizures.[26–28] While studies support LEV's utility in geriatric patients, comprehensive evidence is still emerging.[29] LEV has shown efficacy in elderly patients with cognitive impairment[30] and in reducing late-onset post-stroke seizures.[31] It also outperformed standard ASMs, Valproate and Carbamazepine, as an initial monotherapy for new-onset epilepsy in patients aged ≥60, evidenced by longer treatment duration and better tolerability.[32] Enhancing LEV adherence in the elderly could be achieved by vigilant monitoring of side effects, including NPDs, to prevent treatment discontinuation.

Strengths and Limitations

To the best of our knowledge, this is the inaugural study to delineate the frequency of new-onset neuropsychiatric adverse events in elderly epilepsy patients treated with LEV for a minimum of six months. The study involved decade-long

retrospective data, and identified significant factors correlated with NPDs, offering potential therapeutic insights. However, our research has some limitations. The first major limitation is the retrospective design, which is subject to information bias, including the absence of essential data and missing values for certain variables, thereby restricting the examination of outcomes and associated risk factors. The second notable limitation is a relatively small sample size, resulting in a high type 2 error, which limits the significance of certain statistical associations. The study also did not detail the specific types or severities of NPDs, nor their management strategies. An exploration into how these NPDs influenced patients' decisions to continue treatment would also have been valuable.

Conclusion

While LEV is known to cause neuropsychiatric side effects, the incidence of these side effects seems to be lower in older adults. The concurrent prescription of LEV and carbamazepine/oxcarbazepine may contribute to the emergence of NPDs and warrants careful consideration in this age group. This suggests a cautious approach to using these drugs in combination. More extensive research with larger sample sizes would be valuable in further exploring this critical aspect of patient care. The findings from this study can contribute to refining prescribing practices, enhancing patient safety, and potentially improving the quality of life for older adults dealing with seizure disorders.

Abbreviations

LEV, Levetiracetam; ASMs, antiseizure medications; NPDs, neuropsychiatric disorders.

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