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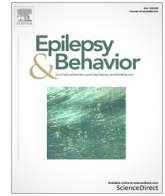
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Dosage, time, and polytherapy dependent effects of different levetiracetam regimens on cognitive function

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ABSTRACT

Objective: Cognitive impairment is a potential drawback of antiseizure medications. This study aimed to evaluate the impact of different levetiracetam drug regimens on cognitive function.

Methods: A retrospective analysis identified 221 patients diagnosed with seizures who underwent cognitive screening. Patients were categorized into four groups: no medications, non-levetiracetam medications, high and low dose levetiracetam. Composite scores determined low and high levetiracetam groups whereby one point was added for each increment in dosage, duration since uptake, and concurrent anti-seizure medication. Variables known to affect cognition were recorded and classified as demographic, seizure-related, diagnosis-related, and psychopathology. Logistic regression was used to identify variables associated with cognitive scores below cut-off.

Results: Multivariable analysis found being male, non-active in the community, less than 12 years of education, left temporal lobe epilepsy, high seizure frequency, and depression were associated with poor cognitive performance. In a final regression analysis, the high levetiracetam group exhibited a 4.5-fold higher likelihood of scoring below cut-off than the medication-free group (OR 4.5, CI 1.5–13.6, $p < .08$). Depression (OR 2.1, CI 1.1–3.9, $p < .03$), being male (OR 2.2, CI 1.1–4.3, $p < .02$), and not being active in the community (OR 3.8, 1.6–8.7, $p < .003$) remained significant contributors to the model. Language ($p < .05$), attention ($p < .05$), and delayed recall ($p < .001$) were the most affected cognitive domains.

Significance: When taken in small doses, for brief periods as monotherapy, levetiracetam minimally influences cognition.

At higher doses, as part of long-term seizure management, in conjunction with multiple ASMs, LEV is associated with cognitive impairment.

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1. Introduction

Levetiracetam (LEV) is a widely used second-generation anti-seizure medication (ASM) with proven efficacy in controlling seizures [1,2]. LEV differs from other ASMs in that it binds to synaptic vesicle protein 2A and alters presynaptic vesicle action [3].

Several negative psychiatric and behavioral side effects have been associated with the drug, including aggression, irritability,

anger, and affective disorders [4–7]. The effects of LEV on cognitive function have received comparatively less attention but are generally favorable. Although some studies have indicated reduced cognitive performance with LEV compared with placebo [8] and in case reports [9], others have reported improvements in attention, memory, and executive function [10–15].

However, isolating the specific effects of medication on cognitive performance remains challenging in clinical neurology populations. Numerous, sometimes interacting factors, such as the affected brain region, socioeconomic status, seizure severity, or mood, can contribute to negative cognitive outcomes [16,17]. Helmstaeder and Witt [27], for example, reported control of sei-

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zures improves cognitive performance, indicating that this factor moderates cognition rather than medication psychotropics specifically. Moreover, the diverse and individualized drug regimens followed by patients further complicate the relationship between medications and cognitive performance. Achieving seizure control often involves experimenting with multiple medications at different doses over varying time periods [18]. In contrast, much of the research investigating the adverse cognitive effects of ASMs compares cognitive performance between individual ASMs, employs small clinical trials conducted over short time scales, or fails to adequately account for significant risk factors for impaired cognition [10,12,14,15].

An alternative approach is to consider the “drug load,” which combines daily dosage and concomitant medications to assess adverse events [19–21]. Although this method has rarely been used to investigate the effects of ASMs on cognition, a recent study calculated “moderate” and “severe” drug loads and reported that higher loads lead to greater suppression in brain areas associated with language [22]. The duration of ASM use is also a relevant factor in drug load assessment, as long-term medication consumption is known to alter the biology and responsiveness of the nervous system [23].

The objective of the present study, therefore, was to examine the effects of different LEV drug loads on cognition and control for known risk factors for impaired cognitive function.

2. Methods

A retrospective chart review was performed on patients diagnosed with seizure disorders by neurologists and/or epileptologists using an electroencephalogram (EEG) at the Epilepsy Monitoring Unit (EMU), Hamad General Hospital, Qatar. Seizure diagnoses conformed to the ILAE definitions [24]. All patients admitted for seizure evaluation were eligible for inclusion, except for those with learning difficulties and/or psychiatric comorbidities. Participants with more than 5% of the data missing were excluded. Cognition was assessed using the Montreal Cognitive Assessment (MoCA) [25], which evaluates visuospatial/executive function, naming, attention, language, orientation, delayed verbal memory, and abstraction. A score of 26 indicates normal functioning, and a point is added for 12 years or less of education. Mood was assessed using the Public Health Questionnaire (PHQ-9) for depression and the Generalized Anxiety Scale (GAD-7) for anxiety, with cut-off scores of 10 or above indicating moderate depression or anxiety. A psychologist or trained nurse conducted all assessments.

Demographic characteristics included sex, age, education, marital status, community-based activity (CBA) (working or studying vs. unemployed or at home), and origin (local vs. expatriate). Diagnoses included left temporal, right temporal, and frontal lobe epilepsies, psychogenic non-epileptic events (PNEE), and ‘other’. Others included juvenile myoclonic, idiopathic generalized, and occipital epilepsies. Where multiple diagnoses were reported, each diagnosis was individually chronicled. Seizure-related variables recorded included seizure onset, seizure freedom, average number of seizures in the last 12 months, seizures within the last 24 hours before testing, and loss of consciousness during an event. Data were divided into four medication groups as follows: no medications (NoMed) (patients newly diagnosed or non-compliant), non-levetiracetam medications (OtherMed), and high and low LEV groups. High and low LEV were calculated using composite scores whereby one point was added for each concomitant ASM (maximum 4 including LEV), one point for each period of use (in months) ($0 < 6$, $6 < 12$, $12 < 24$, 24), and one point for each dosage category in milligrams (mg) per day ($0 < 1000$, $1000 < 2000$, $2000 < 3000$, 3000). The minimum attainable score

was 3 (LEV monotherapy, ≤ 1000 mg per day for ≤ 6 months), and the maximum was 12 (LEV usage > 2 years, reaching a dosage of > 3000 mg per day with three concomitant ASMs). The composite scores were divided into higher and lower groups (3–7 vs. 8–12).

2.1. Statistical analysis

The data were analyzed using IBM SPSS (version 26) [26]. Means and standard deviations were used to describe continuous variables, with frequencies and percentages presented for nominal data. Pearson's Chi-square test and independent sample t-tests were used to explore statistical differences in variables between the medication groups.

Binary logistic regressions were computed to explore the association between predictor variables and binary outcome MoCA scores above or below 26. Four models were built, each including medications as the exposure. The models were based on demographic, diagnosis, seizure-related, and psychiatric categories. Variables associated with low MoCA scores were used to construct a final adjusted regression. Odds ratios (OR) and confidence intervals (CI) are presented. The contribution of each variable in the model was calculated using the change in R^2 after each was added independently.

The Kruskal–Wallis H test was employed to investigate differences in the medication group means in cognitive screening subdomains. Post hoc analysis was conducted using Bonferroni corrections for multiple comparisons.

The confidence level was maintained at 95%, and p -values were considered significant at ≤ 0.05 for all analyses.

3. Results

After inclusion and exclusion criteria were applied, a total of 221 people were included in the analysis. The average age of participants was 30.2 years ± 11.6 . There were more males (53.3%), and 60.0% were ‘locals’ (from Qatar), with the remaining expatriates. The most common diagnosis was left temporal lobe epilepsy (24.3%), and frontal lobe epilepsy was the least (14.3%).

The largest medication category, comprising 79 patients (35.7%), was ‘OtherMed’ (Table 1). Most patients in this group were on monotherapy (53.2%), with valproate (42.9%), oxcarbazepine (35.7%), and topiramate (11.9%) being the leading prescriptions (Supplementary Material A). The remainder of this group were on polytherapy, with lamotrigine (56.8%), carbamazepine (51.6%), and topiramate (24.3%) most often used in combination. The next largest medication groups were the low (61 patients, 27.6%) and high LEV (47 patients, 21.3%) groups. The low LEV group received 65.6% monotherapy compared with 19.1% in the high LEV group (Supplementary Material A). In the low LEV group, carbamazepine (28.6%) and lamotrigine (19.0%) were the most common additional drugs, whereas in the high LEV group, they were lacosamide (31.6%) and lamotrigine (23.7%). Regarding dosage, 80.3% of low LEV patients were on 1000–2000 mg per day, whereas 44.7% of the high LEV group were on more than 3000 mg per day (Table 2). The duration of LEV usage differed between the groups, with 39.4% of the low LEV group using the medication for over two years compared with 76.6% of the high LEV group. The smallest group, ‘NoMed,’ consisted of 34 participants (15.4%).

Differences were found between the characteristics of the medication groups. More locals ($p = 0.04$) and patients with right temporal lobe epilepsy ($p = 0.01$) were found in OtherMed, and more people with PNEE were in the NoMed group ($p = 0.001$). Onset and seizure freedom were both significantly lower for NoMed ($p = 0.004$ and $p = 0.04$, respectively), and the mean MoCA score was lower in the high LEV group ($p = 0.001$) (Table 1).

Table 1
Demographic and clinical characteristics of the cohort.

Category	Variable	N (%) / M ± SD	Medication group				p-value
			NoMed	OtherMed	Low LEV	High LEV	
Medication	–	221 (100)	34 (15.4)	79 (35.7)	61 (27.6)	47 (21.3)	–
Demographic	Female	101 (45.7)	11 (10.9)	38 (37.6)	27 (26.7)	25 (24.8)	0.29
	Age	30.2 ± 11.6	27.5 ± 11.6	30.4 ± 11.6	30.2 ± 12.4	31.7 ± 10.5	0.31
	Local	132 (59.7)	14 (10.6)	49 (37.1)	35 (26.5)	34 (25.8)	0.04*
	Not married	130 (58.8)	24 (18.5)	41 (31.5)	39 (30.0)	26 (20.0)	0.22
	Education ≤12	105 (47.7)	12 (19.4)	40 (38.1)	34 (32.4)	19 (18.1)	0.20
Diagnosis ^β	No CBA	55 (25.0)	7 (12.7)	22 (40.0)	12 (21.8)	14 (25.5)	0.50
	Frontal	36 (14.3)	6 (16.7)	13 (36.1)	8 (22.2)	9 (25.0)	0.85
	R Temporal	52 (20.7)	3 (5.8)	27 (51.9)	10 (19.2)	12 (23.1)	0.01*
	L temporal	61 (24.3)	6 (9.8)	24 (39.3)	16 (26.2)	15 (24.6)	0.48
	Other	54 (21.5)	6 (11.1)	20 (37.0)	17 (31.5)	11 (20.4)	0.73
	PNEE	48 (19.1)	19 (39.6)	11 (22.9)	14 (13.2)	4 (8.3)	0.001
	Onset	9.5 ± 9.1	5.7 ± 7.5	11.0 ± 9.1	7.8 ± 9.0	11.8 ± 9.4	0.004*
Seizure	Frequency	48.6 ± 91.2	80.9 ± 121.8	38.2 ± 70.7	40.1 ± 85.4	53.6 ± 100.1	0.13
	Freedom	8.0 ± 23.4	0.9 ± 1.7	11.9 ± 35.2	9.2 ± 15.4	5.2 ± 11.0	0.04*
	LoC	115 (52.3)	16 (13.9)	41 (35.7)	39 (33.9)	19 (16.5)	0.10
	In last 24 hours	51 (23.1)	9 (17.6)	20 (39.2)	10 (19.6)	12 (23.5)	0.54
	PHQ-9	10.1 ± 6.3	10.8 ± 6.5	9.7 ± 5.7	9.5 ± 6.7	10.7 ± 6.6	0.71
Psychiatric	GAD-7	8.4 ± 5.6	8.4 ± 6.1	8.3 ± 5.3	7.9 ± 5.5	9.2 ± 5.6	0.77
Cognitive	MoCA	23.5 ± 4.3	24.4 ± 4.6	23.3 ± 4.1	24.7 ± 4.1	21.6 ± 4.0	0.001**

Note. LEV=levetiracetam, CBA=community-based activity, ASM=antiseizure medication, R=right, L=left, PNEE=psychogenic non-epileptic events, LoC=loss of consciousness, PHQ=Public Health Questionnaire, GAD=Generalized Anxiety Scale, MoCA=Montreal Cognitive Assessment.

^β Multiple diagnoses recorded independently.

* Significant at $p < 0.05$.

** Significant at $p < 0.001$.

Table 2
Distribution of factors for composite score in levetiracetam users.

Factor	Composite score	Category	Low LEV N (%)	High LEV N (%)
Total daily dose (mg)	1	≤1000	7 (11.5)	1 (2.1)
	2	>1000–≤2000	49 (80.3)	6 (12.8)
	3	>2000–≤3000	4 (6.6)	19 (40.4)
	4	>3000	1 (1.6)	21 (44.7)
Number of ASMs*	1	1	40 (65.6)	9 (19.1)
	2	2	17 (27.9)	17 (36.2)
	3	3	4 (6.6)	17 (36.2)
	4	≥4	0 (0.0)	4 (8.5)
Months taking LEV	1	≤6	17 (27.9)	2 (4.3)
	2	>6 ≤ 12	10 (16.4)	0 (0.0)
	3	>12 ≤ 24	10 (16.4)	9 (19.1)
	4	>24	24 (39.3)	36 (76.6)

Note. mg=milligrams, ASM=antiseizure medication. LEV=levetiracetam. *Including levetiracetam.

The results of the four logistic regression models are shown in Supplementary Material B. In Model 1, medications were adjusted for demographic variables with sex (OR 2.0 CI 1.0–3.8, $p < 0.05$), being non-active in the community (OR 3.4 CI 1.5–8.1, $p < 0.05$), education ≤12 years (OR 2.1 CI 1.0–4.3, $p = 0.04$), and being in the high LEV group (OR 4.1 CI 1.4–12.2, $p < 0.05$) associated with MoCA scores <26. Model 2 included seizure diagnoses with left temporal lobe epilepsy and high LEV found to be associated with cognitive impairment (OR 3.7 CI, 1.1–12.0, $p = 0.03$ and OR 4.7 CI, 1.6–13.8, $p < 0.01$). Right temporal and frontal lobe epilepsy trended toward MoCA below 26 but did not reach significance (both $p = 0.08$). Model 3 included seizure-related variables. Along with being in the high LEV group (OR 4.9 CI, 1.7–14.5, $p < 0.05$), having more than monthly (i.e., 13–52 events) or weekly events (≥52) were associated with poor cognitive screening scores (OR 4.4 CI, 1.1–12.0, $p < 0.05$ and OR 4.5 CI, 1.3–15.5, $p < 0.02$). In Model 4, psychiatric variables were included with moderate depression symptoms (OR 3.1 CI, 1.3–7.4, $p < 0.05$) and being in the high LEV group (OR 4.2 CI, 1.5–12.2, $p < 0.01$) associated with subthreshold MoCA. From the four models, the variables significantly associated with MoCA scores <26 were sex, community-based activity, education, left

temporal lobe epilepsy, seizure frequency, and moderate depression. These were included in a final model, which was statistically significant, $\chi^2(8) = 52.4$, $p < 0.0001$, and explained 28.8% of the variance in cognitive impairment while correctly classifying 74.1% of cases. Patients in the high LEV group were 4.5-fold more likely to score below 26 on MoCA (OR 4.5, CI 1.5–13.6, $p < 0.08$). Elevated depression symptoms (OR 2.1, CI 1.1–3.9, $p < 0.03$), being male (OR 2.2, CI 1.1–4.3, $p < 0.02$), and not active in the community (OR 3.8, CI 1.6–8.7, $p < 0.002$) also contributed to the model (Table 3).

With regard to cognitive domains, significant differences between the medication groups were observed for attention ($H(3) = 9.86$, $p = 0.02$), language ($H(3) = 12.05$, $p < 0.05$), and delayed verbal memory ($H(3) = 19.4$, $p < 0.001$) (Table 4). Patients in the high LEV group produced lower results across all MoCA subdomains except for orientation. Post hoc analysis revealed significantly lower scores for attention and language ($p = 0.027$ and $p = 0.006$) in the high LEV group compared with OtherMed. In the delayed verbal memory task, high LEV patients scored significantly lower than both NoMed and OtherMed ($p = 0.003$ and $p = 0.001$).

Table 3

Fully adjusted model with medication as the exposure and MoCA score the outcome.

Variable		MoCA < 26 (%)	Wald	p-value	OR (CI)	ΔR^2
Medication	NoMed	17 (50.0)	11.7	0.009*		0.65
	OtherMed	26 (32.9)	2.5	0.12	2.1 (0.8–5.4)	
	Low LEV	33 (54.1)	0.005	0.94	1.0 (0.4–2.5)	
	High LEV	38 (80.9)	7.0	0.008*	4.5 (1.5–13.6)	
Sex	Male	66 (65.3)	5.3	0.02*	2.2 (1.1–4.3)	0.27
	Female	70 (58.3)				
CBA	Non active	44 (80.0)	9.6	0.002*	3.8 (1.6–8.7)	0.53
	Active	92 (55.8)				
Education	≤12 years	81 (70.4)	3.4	0.07	1.8 (1.0–3.4)	0.16
	>12 years	55 (52.4)				
Frequency‡	0–2	36 (53.7)	7.3	0.06		0.37
	3–12	32 (52.5)	1.5	0.23	0.6 (0.3–1.4)	
	13–52	38 (73.1)	0.8	0.38	1.5 (0.6–3.7)	
	53+	36 (73.2)	2.1	0.15	2.0 (0.8–5.4)	
Left temporal	Yes	44 (72.1)	0.4	0.13	1.8 (0.8–3.6)	0.28
	No	92 (61.5)				
Depression	PHQ-9 ≥10	79 (69.9)	5.0	0.03*	2.1 (1.1–3.9)	0.25
	PHQ-9 < 10	57 (52.8)				

CBA=community-based activity, OR=odds ratio, CI=confidence interval, PHQ=Public Health Questionnaire.

Model summary for multivariable analysis: – 2 Log likelihood = 240.20.

Cox and Snell R square = 0.21, Nagelkerke R square = 0.29, Hosmer and Lemeshow, Chi-square value = 2.60, $p = 0.98$. ΔR^2 = relative change in R^2 through the addition of each variable.

‡Average number of events per year.

* Significant at $p < 0.05$.**Table 4**

Mean and standard deviation of MoCA scores for different cognitive domains by drug group.

Cognitive domain	Drug group				
	High LEV Mean (SD)	Low LEV Mean (SD)	OtherMed Mean (SD)	NoMed Mean (SD)	All Mean (SD)
^a Executive/Visuospatial	3.7 (1.2)	4.0 (1.0)	3.9 (1.1)	3.8 (1.1)	3.9 (1.1)
^b Naming	2.7 (0.5)	2.8 (0.4)	2.8 (0.4)	2.8 (0.4)	2.8 (0.4)
^a Attention	4.6 (1.4)*	5.2 (1.3)	4.9 (1.6)	5.2 (1.3)	5.0 (1.4)
^c Language	1.0 (1.0)*	1.6 (0.9)	1.4 (0.9)	1.6 (1.0)	1.4 (1.0)
^c Abstraction	1.2 (0.8)	1.5 (0.6)	1.4 (0.7)	1.4 (0.7)	1.4 (0.7)
^d Delayed verbal memory	2.1 (1.6) [†]	3.3 (1.5)	2.7 (1.6)	3.4 (1.5)	2.8 (1.6)
^a Orientation	5.8 (0.5)	5.8 (0.5)	5.7 (0.7)	5.7 (0.6)	5.7 (0.6)

Note. LEV=levetiracetam. [†]Significant at $p < 0.001$. *Significant at $p < 0.05$ Maximum a=6, b=3, c=2, d=5.

4. Discussion

This study explored the effects of different LEV drug load regimens on cognitive function while controlling for multiple risk factors for poor cognition. Our findings align with previous studies that reported no association between cognitive dysfunction and low-dose LEV monotherapy over short time periods. Improvements in cognition that have been reported elsewhere were not observed [11,13,14]. In contrast, we report a 4.5-fold increase in the likelihood of subthreshold MoCA scores in high LEV patients compared with those in the no-medication group. These patients tended to be male, exhibit symptoms of depression, and have low community activity.

The core cognitive domains affected in the high LEV group, attention, language, and delayed verbal recall, reflect other studies of ASM use and cognitive dysfunction.

The dominant factor in the high LEV group was dosage, with 85.1% of patients taking 2000 mg or more per day and 44.7% receiving 3000 mg or more. Increases in LEV dosage are not known to cause cognitive issues and may improve aspects of cognition [27,28]. Wandschneider and colleagues [29] for example, reported that incremental doses of LEV deactivated diseased hippocampi in a stepwise fashion, leading to improved visual-spatial and verbal task performance. Other studies indicate no adverse events at LEV doses of 2000 or 3000 mg although cognition was not directly tested in these works [30,31]. In contrast, animal models provide

evidence of levetiracetam-induced impaired memory at high doses [32]. These findings indicate there is a discernible threshold at which cognitive functioning is detrimentally impacted by LEV. Our data show an association between high LEV doses and cognitive deficits, but only in combination with other factors.

One factor is the number of concomitant ASMs. More than one-third of high LEV patients were on three or more medications (38.3%). In this regard, our data support the frequently reported negative relationship between multiple ASMs and cognitive function [33,34]. Polytherapy is understood to increase the risk of unwanted interactions, including effects on cognition [35,36]. However, LEV is generally considered to be a better-tolerated add-on drug with rare negative drug interactions [27,37]. Otoul and colleagues [38] tested LEV against valproic acid, lamotrigine, carbamazepine, and topiramate and found no clinically meaningful changes in plasma concentrations of any ASM. Nevertheless, human and animal models indicate that LEV increases the potency of concomitant medications, including drugs known to cause cognitive problems such as carbamazepine and topiramate [39–41]. This may partially explain the current findings, as carbamazepine and topiramate account for over one-quarter of polytherapy in the high LEV group, although a comparable ratio was registered in OtherMed. Similar to our results, in a study in which LEV was the most prescribed ASM, each additional concomitant medication increased concentration and memory problems [42].

The duration of ASM use is a further consideration in our findings. Seventy-seven percent of the high LEV group had been taking the drug for 24 months or more. Many studies reporting improved cognition after LEV administration are less than one year in duration [10,13,15,43]. In contrast, the average LEV usage for patients in this study was 11.8 years in the high group and 7.4 years in the low group (11.0 years for the OtherMed group). Long-term use of ASMs may indicate good seizure control, which is associated with positive cognitive outcomes [27]. However, it may also indicate refractory seizures and an increased risk of polypharmacy [19,44]. It is important to note that in this study, a significant proportion of the low LEV (39%) and OtherMed groups (57%, data not shown) were also longstanding users of ASMs without experiencing the same cognitive deficits.

This study also revealed that male individuals displaying depressive symptoms with limited involvement in community activities were more likely to score low on MoCA. Depression is a widely acknowledged risk factor for cognitive impairment and is also associated with LEV use [17,45,46]. However, the etiology of depression in seizure disorders is multifaceted, encompassing factors such as unemployment and social withdrawal [47]. Despite the difficulty in unraveling the influence of each factor, addressing depression or targeting work and social engagement may be a viable approach to enhancing cognition in these patients. The significance of employment may be particularly notable for men who report heightened levels of depression when confronted with unemployment, possibly due to societal expectations of masculinity [48].

This study adopted a distinct approach to investigate the impact of LEV on cognition by examining drug load. By focusing on the interplay between dosage, duration, and polytherapy, this work sheds light on their collective influence on cognition. For instance, it is noteworthy that nearly 20% of high LEV patients were undergoing monotherapy, implying that both duration and dosage can contribute to cognitive impairments similar to those associated with polypharmacy. Likewise, approximately 15% of high LEV patients were administered LEV doses below 2000 mg, suggesting that concomitant medication and duration play a more influential role in cognitive dysfunction for this subgroup. Consequently, this study highlights that distinct LEV drug load regimens can yield comparable outcomes in terms of cognitive dysfunction, thereby advocating for personalized approaches to seizure management strategies.

4.1. Limitations

This study was a retrospective analysis of prospectively collected data; therefore, collection and registration bias may be present. It is not possible to determine causality from this type of data. Multiple factors related to cognitive dysfunction were included; however, the retrospective nature of the study meant that some relevant variables were omitted. The MoCA is a cognitive screening tool, and it is not known how patients would perform under more extensive neuropsychological evaluation. Similarly, psychiatric evaluations used screening instruments rather than clinical diagnoses. The selection of screening tools was limited by the retrospective nature of this work. Some variables relied on self-reporting over long periods of time, which may have introduced bias and/or a lack of accuracy.

5. Conclusion

In small doses over short time periods, without the presence of simultaneous ASMs, LEV is minimally associated with poor cognition. At higher doses, as part of long-term seizure management and

in conjunction with multiple ASMs, LEV is associated with cognitive impairment, specifically in the domains of memory, language, and attention. Regular cognitive screening for patients on high-levetiracetam regimens is recommended.

6. Ethics approval

The study adhered to the tenets of the declaration of Helsinki and was approved by the Institutional Review Board (MRC-01-20-1152). Consent requirement was waived due to retrospective study design.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.yebeh.2023.109453>.

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