



Assessment of psychiatric and behavioral adverse effects of antiepileptic drugs monotherapy: Could they have a neuroendocrine correlation in persons with epilepsy?

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ABSTRACT

Objective: The study investigated overall adverse event (AE) burden and specifically psychiatric and behavioral side effects (PBAEs) in persons with epilepsy (PWE) on antiepileptic drugs (AEDs) monotherapy. It also assessed their correlation with neuroendocrine and oxidative stress biomarkers.

Methods: This cross-sectional observational study was conducted at a tertiary care hospital between 2016 and 2018. Persons with epilepsy above 18 years on monotherapy of levetiracetam (LEV) and conventional AEDs (carbamazepine (CBZ), phenytoin (PHT), or valproate (VPA)) for at least 6 months were enrolled. Validated questionnaires, 'Mini-International Neuropsychiatric Interview (MINI 7.02)', 'Depression, Anxiety, and Stress Scale 21 (DASS-21)', 'Buss-Perry Aggression Questionnaire (BPAQ)', 'patient-weighted Quality of life Index in Epilepsy (QOLIE-10)', 'Pittsburgh Sleep Quality Index (PSQI)', and 'Liverpool Adverse Events Profile (LAEP)' were used to assess the PBAEs, quality of life, sleep quality, and AE profile. A subgroup of PWE recruited consecutively were considered for estimation of the following neuroendocrine biomarker levels: brain-derived neurotrophic factor (BDNF), homovanillic acid (HVA), 5-hydroxyindoleacetic acid (5-HIAA), and total antioxidant capacity (TAC) which were then correlated with scores of above questionnaires.

Results: After screening 220 PWE, 163 PWE (58 on LEV and 105 on conventional AEDs) with a mean age of 29 ± 10 years were enrolled. Mini-International Neuropsychiatric Interview revealed that LEV group had higher association with PBAEs and lower quality of sleep compared to conventional AEDs ($p = 0.032$ and 0.046 , respectively). Other scales did not show significant difference between LEV and conventional AEDs. In the subset of PWE ($n = 74$, 36 on LEV and 38 on conventional AEDs), LEV group had more association with the PBAEs ($p = 0.010$), higher physical aggression and anger components of BPAQ ($p = 0.03$ and 0.02 , respectively), and more AE ($p = 0.049$) than conventional AED group. However, there was no significant difference in neuroendocrine biomarker levels.

Conclusion: Levetiracetam had a higher association with PBAEs and more AE when compared to conventional AEDs. There was no differential correlation of AEDs with the following neuroendocrine markers: BDNF, HVA, 5-HIAA, and TAC. These facts necessitate exploration of other mechanisms for LEV-induced PBAEs.

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Abbreviations: 5-HIAA, 5-hydroxyindoleacetic acid; AE, adverse event; AEDs, antiepileptic drugs; BPAQ, Buss-Perry Aggression Questionnaire; BDNF, brain-derived neurotrophic factor; DASS-21, Depression, Anxiety, and Stress Scale 21; HVA, homovanillic acid; LAEP, Liverpool Adverse Events Profile; MINI 7.02, Mini-International Neuropsychiatric Interview; QOLIE-10, patient-weighted Quality of life Index in Epilepsy; PWE, persons with epilepsy; PSQI, Pittsburgh Sleep Quality Index; PBAEs, Psychiatric and behavioral adverse effects.

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1. Introduction

Epilepsy is a common neurological disorder that is markedly associated with cognitive, neurological, and psychiatric comorbidities, adversely affecting the quality of life in persons with epilepsy (PWE) [1]. The primary focus of antiepileptic drug (AED) therapy is to control seizures but its effect on comorbid conditions is still doubtful. Previous studies have illustrated high prevalence of emotional {depression (8%–25%), anxiety (17%–63%)}, and behavioral {attention-deficit hyperactivity disorder (30%–40%)} symptoms in epilepsy because of multifactorial etiologies including adverse effects of AEDs [2–6]. Although AEDs are the main stay of treatment, seizures can be controlled in only two-third of the cases with the use of conventional AEDs [7]. Refractoriness

to conventional AEDs results in the expanded use of newer AEDs in PWE. The favorable pharmacological profile of levetiracetam (LEV) over conventional AEDs is that it does not mandate serum drug monitoring (except in pregnancy) because of wide safety margin as well as few interactions with other anticonvulsants, making it a first-line or adjunctive therapy for epileptic seizure [8]. Although a large number of previous studies have demonstrated the increasing use of LEV with respect to its better efficacy profile [9], there are studies highlighting its safety concerns [10]. About 15–20% of adult PWE taking AEDs experience psychiatric and behavioral adverse effects (PBAEs); these include depressive mood, psychosis, increase in irritability, and aggressive behavior. Among AEDs, LEV has a higher association (10–24%) with PBAEs, making it a primary reason for its discontinuation [10]. Levetiracetam has minimal drug interactions owing to its unique mechanism of action [by binding to vesicular protein: synaptic vesicle protein 2A (SV2A) and thereby reducing the neurotransmitter release]. Previous literature has shown that the higher risk of developing PBAEs attributed to LEV is possibly related to a genetic predisposition [11]. However, there is no definite cause for establishing its association with PBAEs. As per established facts, depression and psychiatric disorders have a strong association with alteration in brain-derived neurotrophic factor (BDNF), dopamine and serotonin-like neurotransmitters, and oxidative stress. Serum BDNF levels were found to be lower in patients having major depressive disorders and psychotic disorder like schizophrenia [12]. Similarly, plasma homovanillic acid (HVA) level was found to be decreased in patients with depression [13] and was elevated in those with psychosis [14]. Plasma level of 5-hydroxyindoleacetic acid (5-HIAA) was increased in patients with depression [13], and the total antioxidant capacity (TAC) was reduced in patients with depression and schizophrenia [15]. The current study aimed to identify the overall AE (adverse event) burden specifically for PBAEs in PWE on AED monotherapy and to investigate their relationship with neuroendocrine and oxidative stress biomarkers such as BDNF, HVA, 5-HIAA, and TAC. Correlational analysis of PBAEs and the corresponding biomarkers can help in understanding the mechanism of AEDs-induced AE and may guide in predicting response to AED therapy.

2. Materials and methods

2.1. Study subjects

This cross-sectional observational study was conducted at a tertiary care hospital between 2016 and 2018. The study protocol was approved by the Institute Ethics Committee (IECPG-412/29.06.2016, RT-14/27.07.2016), and registered in Clinical Trial Registry of India (CTRI/2017/10/009997). The study was conducted in accordance with Indian Council of Medical Research ethical guidelines for biomedical research and Indian Good Clinical Practice guidelines. Persons with epilepsy attending the epilepsy clinic, above 18 years of age, on monotherapy of LEV and conventional AEDs (CBZ [carbamazepine], PHT [phenytoin], VPA [valproate]) for at least 6 months, and willing to give informed consent were included in the study irrespective of gender. Persons with epilepsy who were pregnant or seeking pregnancy, who denied for providing blood samples, PWE with status epilepticus, clinically diagnosed with any other neurological, psychiatric disorder, or epileptic syndromes like mesial temporal lobe epilepsy, chronic inflammatory disorder, on drugs known to alter seizure threshold, and PWE with significant hepatic and renal impairment that may require dose alteration were excluded from the study.

2.2. Study data collection

After enrolment, a detailed history of seizure type, AED treatment, and demographic characteristics of the PWE were recorded in a standardized case record form. Then, a panel of validated questionnaires was used to assess the PBAEs, quality of life, sleep quality, and AE profile.

During the latter part of the study, a subgroup of PWE recruited consecutively were considered for estimation of neuroendocrine biomarker levels, which were then correlated with scores of questionnaire-based assessment of neuropsychiatric ADRs with 'adverse effects and quality of life. From these subjects, 5 ml of blood sample was collected and processed further for neuroendocrine markers estimation using enzyme-linked immunosorbent assay (ELISA) kits.

2.3. Assessment of PBAEs using questionnaires

For identification of PBAEs, well-validated and widely used diagnostic questionnaires and scales were applied. Permission to use the scales, if needed, was obtained before initiation of the study.

2.3.1. Mini-International Neuropsychiatric Interview (MINI 7.02)

Mini-International Neuropsychiatric Interview (MINI) was used for diagnosing multiple neuropsychiatric disorders pertaining to the modules of major depression, suicidality (or suicidal behavior), manic (or hypomanic), panic disorder, agoraphobia, obsessive-compulsive disorder (OCD), and psychotic disorders and mood disorders with psychotic features. The MINI is a structured diagnostic interview instrument and employed by mental health professionals and health organizations in more than 100 countries. The questionnaires of MINI were translated into local language for maintaining uniformity during interview. The MINI module includes a systematic and useful series of questions that could be included in a clinical interview when screening for depression and psychiatric comorbidity in a busy clinical setting. There are separate modules for each psychiatric disorder. First two questions of every module were for screening, and if the answer to both questions was yes, then further assessment was done in each module to diagnose the case [16].

2.3.2. Depression, Anxiety, and Stress Scale 21 (DASS-21)

Depression, Anxiety, and Stress Scale 21 (DASS-21) is a set of three self-report scales designed to quantitatively measure the negative emotional states, i.e., depression, anxiety, and stress. It has been widely employed to assess relationship and effect of depression, anxiety, and stress among various populations, age groups, clinical, and nonclinical respondents. In each item, the respondents are supposed to rate the extent to which they have experienced the given state over the past week, using a 4-point severity/frequency scale. In the present study, the Hindi version of DASS-21 was used. As recommended, the obtained scale scores were multiplied by 2, to make them comparable to the DASS normative data scores. For each category like depression, anxiety, and stress, 7 questions were considered, and the maximum score for each would be 42. There are DASS severity ratings to classify each of these into normal (low score), mild, moderate, severe, and extremely severe condition (higher score) [17].

2.3.3. Buss-Perry Aggression Questionnaire (BPAQ)

For quantitatively assessing aggression (physical, verbal, anger, hostility), BPAQ (Buss-Perry Aggression Questionnaire) is a popular 29-item self-rated questionnaire that aims to elicit various domains of aggression. The participants rank certain statements along a 5-point continuum from "extremely uncharacteristic of me" to "extremely characteristic of me." The scale comprises 9 items related to physical aggression, 5 items related to verbal aggression, 7 items related to anger, and 8 items related to hostility, thus comprising four subscales. The participants rank certain statements on a 5-point Likert scale, ranging from 1 (extremely uncharacteristic of me) to 5 (extremely characteristic of me). The total score of overall scale ranges from 9 to 45, with higher scores corresponding to higher levels of trait aggressivity. Similarly, high score for any subitem of the scale indicates that an individual has aggressive behavior to that factor [18].

Table 1
Demographic, seizure, and AED treatment parameters among PWE enrolled in the study.

Parameters	Total PWE (n = 163) Number (percentage)	PWE on conventional AED (n = 105) Number (percentage)	PWE on newer AED (n = 58) Number (percentage)	p-Value
Demographic characteristics:				
Age				
18–35 years	132 (80.98)	83 (79.04)	49 (84.48)	0.291
>35 years	31 (19.01)	22 (20.95)	9 (15.51)	
Sex				
Male	91 (55.82)	72 (68.57)	19 (32.75)	<0.000
Female	72 (44.17)	33 (31.42)	39 (67.24)	
Education				
Undergraduate	63 (38.65)	37 (35.23)	26 (44.82)	0.228
Graduate	100 (61.34)	68 (64.76)	32 (55.17)	
Monthly household income				
<15,000 INR	51 (31.28)	32 (30.47)	19 (32.75)	0.763
≥15,000 INR	112 (68.71)	73 (69.52)	39 (67.24)	
B) Seizure related				
Type of epilepsy				
Focal onset	45 (27.60)	32 (30.47)	13 (22.41)	0.270
Generalized onset	118 (72.39)	73 (69.52)	45 (77.58)	
Duration of epilepsy				
<10 years	103 (63.19)	64 (60.95)	39 (67.24)	0.425
≥10 years	60 (36.80)	41 (39.04)	19 (32.75)	
Seizure frequency at onset of epilepsy				
≤1 attack/year	78 (42.85)	50 (47.61)	28 (48.27)	0.935
>1 attack/year	85 (52.14)	55 (52.38)	30 (51.72)	
Seizure frequency per person in last 6 months				
	0.60 (98/163)	0.51 (54/105)	0.75 (44/58)	0.135
Type of AED treatment (dose range among PWE in mg/day)				
Valproate (n = 53)	750–2000	750–2000		–
Carbamazepine (n = 31)	600–1800	600–1800		–
Phenytoin (n = 21)	300–400	300–400		–
Levetiracetam (n = 58)	1000–3000		1000–3000	–

PWE (person with epilepsy), AEDs (antiepileptic drugs), INR (Indian Rupee)

Table 2
Comparison of PBAE PWE on the basis of MINI modules.

MINI scale	Total PWE (n = 163) (%)	PWE on LEV (n = 58) (%)	PWE on conventional AEDs (n = 105) (%)	p-Value
Overall MINI ^a				
Present	80 (49.07)	35 (60.35)	45 (42.85)	0.032
Absent	83 (50.92)	23 (39.65)	60 (57.14)	
Major depressive episode				
Present	54 (33.12)	21 (36.20)	33 (31.42)	0.534
Absent	109 (66.87)	37 (63.79)	72 (68.57)	
Suicidality				
Present	18 (11.04)	8 (13.79)	10 (9.52)	0.405
Absent	145 (88.95)	50 (86.20)	95 (90.47)	
Mania and hypomania episode				
Present	12 (7.3)	3 (5.17)	9 (8.57)	0.426
Absent	151 (92.63)	55 (94.82)	96 (91.42)	
Panic disorder				
Present	34 (20.85)	10 (17.24)	24 (22.85)	0.398
Absent	129 (79.14)	48 (82.75)	81 (77.14)	
Agoraphobia				
Present	32 (19.63)	16 (27.58)	16 (15.23)	0.022
Absent	131 (80.36)	36 (62.06)	89 (84.76)	
Obsessive-compulsive disorder				
Present	12 (7.36)	4 (6.89)	8 (7.61)	0.865
Absent	151 (92.63)	54 (93.10)	97 (92.38)	
Psychotic disorders and mood disorders with psychotic features				
Present	9 (5.52)	2 (3.44)	7 (6.66)	0.389
Absent	154 (94.47)	56 (96.55)	98 (93.33)	

MINI (Mini-International Neuropsychiatric Interview), PWE (person with epilepsy), LEV (levetiracetam), AEDs (antiepileptic drugs).

^a Overall MINI, i.e., at least one type of psychiatric and behavioral adverse effects (PBAEs) as per MINI modules.

2.3.4. Patient-weighted Quality of life Index in Epilepsy (QOLIE-10)

Patient-weighted Quality of life Index in Epilepsy (QOLIE-10) is a brief survey consisting of 10 questions which are based on health and daily activities of PWE and assesses parameters like energy, emotions, daily activities, mental functions, medication effects, worry about seizures, and overall quality of life. The maximum score of QOLIE-10 is 5, higher scores represent poorer quality of life [19].

2.3.5. Pittsburgh Sleep Quality Index (PSQI)

Pittsburgh Sleep Quality Index (PSQI) is a scale to assess the quality of sleep of the subjects. It contains 19 self-rated questions, 5 questions rated by the bed partners or roommate. Components to be assessed by PSQI are subjective sleep quality, sleep latency, sleep duration, habitual sleep efficacy, sleep disturbances, use of sleep medications, and daytime dysfunction. Maximum score of PSQI is 18, and total score of ≥5 is indicative of poor sleep quality [20].

2.3.6. Liverpool Adverse Events Profile (LAEP)

Adverse event assessment was done with the help of Liverpool Adverse Events Profile (LAEP) scoring during the 6 months follow-up period. The LAEP is a scale developed to quantify patients' perceptions of the side effects because of AED treatment. There is a checklist of symptoms experienced in the past 4 weeks that are rated using Likert scale. Liverpool Adverse Events Profile has been used primarily to report the frequency of specific AE, and the higher score represents more AE with a maximum score of 76 [21].

2.4. Assessment of neuroendocrine markers and antioxidant status

Serum levels of the following neuroendocrine biomarkers were assessed with the help of ELISA kits: BDNF (Bolster Biological Technology Co. Ltd., CA, USA), HVA and 5-HIAA (Sincere Biotech, Beijing, China), and TAC (Bioassay Systems, CA, USA). Total antioxidant capacity is expressed as μM Trolox equivalents' units as mentioned in the brochure of ELISA kit. Detection range is mentioned as 1.5 to 1000 μM Trolox equivalents. Venous blood (5 ml) was drawn and was put in serum separation vacutainer. Thereafter, the serum was separated by centrifugation at 3500 rpm for 10 min at 4 °C. Separate aliquots were

Table 3
BPAQ, DASS-21, QOLIE-10, PSQI, and LAEP scores compared in total patients on LEV and conventional AEDs.

BPAQ															
	Physical aggression			Verbal aggression			Anger			Hostility			BPAQ score		
	Median (IQR)	Mean	p-Value	Median (IQR)	Mean	p-Value	Median (IQR)	Mean	p-Value	Median (IQR)	Mean	p-Value	Median (IQR)	Mean	p-Value
LEV N = 58	13.00 (9.00–21.00)	16.53	0.841	11.00 (5.00–17.00)	11.26	0.905	14.00 (7.00–24.25)	16.00	0.896	12.00 (8.00–24.00)	16.36	0.458	53.00 (29.00–84.25)	60.16	0.640
Conventional N = 105	13.00 (9.00–20.50)	16.81		11.00 (5.00–14.50)	11.35		12.00 (7.00–22.00)	15.54		16.70 (8.00–24.00)			53.00 (33.00–82.00)	60.41	
DASS-21															
	Depression			Anxiety			Stress			DASS-21 score			QOLIE-10 score		
	Median (IQR)	Mean	p-Value	Median (IQR)	Mean	p-Value	Median (IQR)	Mean	p-Value	Median (IQR)	Mean	p-Value	Median (IQR)	Mean	p-Value
LEV N = 58	4.00 (0.00–11.00)	6.61	0.632	4.00 (1.75–9.00)	6.05	0.417	3.50 (0.00–12.00)	6.07	0.482	10.00 (3.00–36.00)	18.62	0.350	2.20 (1.70–2.82)	2.29	0.395
Conventional N = 105	3.00 (0.00–11.50)	6.12		4.00 (0.00–11.00)	5.94		3.00 (0.00–10.00)	5.58		10.00 (0.00–33.50)	17.65		2.10 (1.60–2.80)	2.41	
PSQI score															
	PSQI score			LAEP score											
	Median (IQR)	Mean	p-Value	Median (IQR)	Mean	p-Value									
LEV N = 58	4.00 (2.00–6.00)	4.42	0.046	31.00 (24.00–37.00)	32.33	0.102									
Conventional N = 105	3.00 (2.00–5.00)	3.61		27.00 (23.50–37.00)	30.19										

IQR (interquartile range), BPAQ (Buss–Perry Aggression Questionnaire), DASS-21 (Depression, Anxiety, and Stress Scale 21), QOLIE-10 (patient-weighted Quality of life Index in Epilepsy), PSQI (Pittsburgh Sleep Quality Index), LAEP (Liverpool Adverse Events Profile).

Table 4
Comparison of PWE subset on the basis of MINI modules.

MINI parameters	PWE on LEV (n = 36)		PWE on conventional AEDs (n = 38)		p-Value
	Present (%)	Absent (%)	Present (%)	Absent (%)	
1. Overall MINI	23 (63.88)	13 (36.11)	13 (34.21)	25 (65.78)	0.010
2. Major depression	13 (36.11)	23 (63.88)	10 (26.31)	28 (73.68)	0.362
3. Suicidality	5 (13.88)	31 (86.11)	2 (5.26)	36 (94.73)	0.205
4. Mania	2 (5.55)	34 (94.44)	2 (5.26)	36 (94.73)	0.955
5. Panic disorder	4 (11.11)	32 (88.88)	3 (7.89)	35 (92.10)	0.636
6. Agoraphobia	11 (30.55)	25 (69.44)	7 (18.42)	31 (81.57)	0.223
7. Obsessive-compulsive disorder	2 (5.55)	34 (94.44)	1 (2.63)	37 (97.36)	0.523
8. Psychotic disorders	0	36	1	37	–

MINI (Mini-International Neuropsychiatric Interview), PWE (person with epilepsy), LEV (levetiracetam), AEDs (antiepileptic drugs).

made for the estimation of different parameters and stored at $-80\text{ }^{\circ}\text{C}$ till analysis.

2.5. Statistical analysis

Enrolled PWE were classified into 2 groups, i.e., PWE on LEV monotherapy and PWE on conventional AEDs monotherapy (CBZ, PHT, or VPA). Results were analyzed using Statistical Package for the Social Sciences (SPSS) for Windows, version 23 (IBM Corp., Armonk, N.Y., USA). Data were expressed as mean \pm standard deviation (SD) or in percentage for parametric data and in median and range for nonparametric data. Student's *t*-test was used for parametric data comparison, and Mann-Whitney *U* test was used for nonparametric data comparison. Spearman's rank correlation coefficient was used to find out the correlation between scores of different scales, i.e., MINI, DASS-21, BPAQ, QOLIE-10, LAEP, and PSQI. *p*-Value ≤ 0.05 was considered for statistical significance.

3. Results

After screening 220 PWE, this study enrolled 163 PWE with a mean age of 29 ± 10 years and included 55.82% male subjects. Among the enrolled PWE, 72.4% had generalized seizures, and 27.6% had focal seizures; 58 were on LEV and 105 were on conventional AED monotherapy. Both LEV and conventional AEDs groups exhibited similar demographic and seizure-related characteristics (Table 1).

3.1. Questionnaire-based assessment of PBAE in PWE

According to MINI scale, LEV monotherapy group had a significantly higher association with PBAEs (overall MINI, i.e., at least one type of PBAEs as per MINI modules) when compared to conventional AEDs ($p = 0.032$). However, when MINI modules were individually compared in between the two groups, no significant difference was found except for higher agoraphobia association with LEV group ($p = 0.022$) (Table 2). On comparing the BPAQ, DASS-21, QOLIE-10, and LAEP scores among LEV and conventional AED groups, no significant difference was found. Persons with epilepsy on conventional AEDs were having significantly better quality of sleep according to PSQI score as compared to PWE on LEV ($p = 0.046$), though in both groups, median PSQI scores were < 5 , which did not fulfill the criteria of poor quality of sleep (Table 3).

In a subset of PWE ($n = 74$), which were considered for neuroendocrine markers assessment, 36 were on LEV monotherapy, while 38 were on conventional AEDs. On the basis of MINI modules, association of PBAEs among this subset of PWE (percentage wise) revealed similar trend to that of total PWE ($n = 163$). The LEV monotherapy group in this subset had an increased association with the PBAEs (at least one type of PBAEs as per MINI modules) than conventional AED group ($p = 0.010$). There was no significant difference when individual MINI

modules were compared separately between LEV and conventional AED groups (Table 4).

In the subset of PWE, comparison among LEV and conventional AEDs was also done on the basis of BPAQ, DASS-21, QOLIE-10, PSQI, and LAEP questionnaires' scores. The PWE in LEV group had significantly higher physical aggression and anger components of BPAQ ($p = 0.03$ and 0.02 , respectively) than conventional AEDs. The analysis of AE profile using LAEP scores showed significantly more AE in LEV group ($p = 0.049$) (Table 5).

3.2. Neuroendocrine parameters assessment in PWE

Neuroendocrine parameters (BDNF, 5-HIAA, HVA) and TAC level assessment among the subset of PWE with presence of any PBAEs (at least one type of PBAEs as per MINI modules) and absence of PBAEs did not reveal any significant difference. Similarly, the comparison between LEV and conventional AEDs groups did not reveal any significant difference in biomarker level (Table 6).

3.3. Correlation between BPAQ, DASS-21, QOLIE-10, PSQI, and LAEP scores

The questionnaire scores were correlated among all PWE ($n = 163$), and strong intrascale correlation was found within the components of BPAQ and DASS-21. Among different scales, the intercorrelation revealed that hostility component of BPAQ was moderately associated with anxiety, stress components, and total scores of DASS-21 questionnaire. The QOLIE-10 score was highly correlated with LAEP score, which showed that PWE with higher adverse effects had a poor quality of life (Table 7).

4. Discussion

This study had explored the association of PBAEs among PWE on monotherapy of newer AEDs (e.g., LEV) in comparison to conventional AEDs (CBZ, VPA, or PHT). The study also attempted to correlate the presence of PBAEs with the levels of neuroendocrine markers and antioxidant status. This study has shown an increased association of PBAEs among PWE on LEV than conventional AEDs treatment as per MINI scale. One of the recent studies has concluded that more comorbid psychiatric conditions occurred in some epilepsy syndromes (e.g., mesial temporal lobe epilepsy) [22]. However, these subjects were not included in our study so adverse effects reported mostly correlated with the AED therapy. As per previous studies, PBAEs due to AEDs are not only responsible for discontinuation of the treatment in up to 25% of PWE, but also these comorbidities lead to suboptimal dosing, poor adherence, and thus, adversely affect the quality of life of PWE [23,24]. As all the subjects were on recommended dose range, the correlation of AEDs and dosage was not done. Along with the AE, the cost of treatment is a major contributor for noncompliance to AEDs treatment in epilepsy. In a developing country like India, cost of treatment is a major limitation; moreover,

Table 5
BPAQ, DASS-21, QOLIE-10, PSQI, and LAEP scores compared in subset of PWE on LEV and conventional AEDs.

BPAQ															
	physical aggression			Verbal aggression			Anger			Hostility			BPAQ score		
	Median (IQR)	Mean	p-Value	Median (IQR)	Mean	p-Value	Median (IQR)	Mean	p-Value	Median (IQR)	Mean	p-Value	Median (IQR)	Mean	p-Value
Levetiracetam N = 36	13.50 (9.00–21.00)	17.41 ± 10.09	0.030	13.00 (5.00–17.00)	12.22 ± 6.27	0.057	15.50 (7.00–26.75)	17.50 ± 9.88	0.022	14.00 (8.00–24.75)	17.25 ± 10.21	0.118	61.00 (29.25–95.00)	64.38 ± 34.00	0.061
Conventional N = 38	9.00 (9.00–16.25)	13.21 ± 6.92		7.50 (5.00–13.00)	9.34 ± 5.40		7.00 (7.00–16.25)	12.65 ± 7.97		9.00 (8.00–16.25)	13.52 ± 7.44		33.50 (29.00–63.50)	48.73 ± 26.12	
	Depression			Anxiety			Stress			DASS-21 score			QOLIE-10		
	Median (IQR)	Mean	p-Value	Median (IQR)	Mean	p-Value	Median (IQR)	Mean	p-Value	Median (IQR)	Mean	p-Value	Median (IQR)	Mean	p-Value
Levetiracetam N = 36	3.00 (0.00–9.00)	5.97 ± 7.31	0.396	3.00 (1.00–9.00)	5.55 ± 5.76	0.190	3.00 (0.00–9.00)	5.66 ± 6.28	0.200	9.50 (3.00–29.50)	17.19 ± 18.49	0.124	2.10 (1.60–2.75)	2.15 ± 0.679	0.485
Conventional N = 38	0.00 (0.00–8.00)	4.71 ± 6.83		1.50 (0.00–7.75)	4.60 ± 6.05		1.50 (0.00–7.50)	4.34 ± 5.72		4.00 (0.00–20.50)	13.65 ± 17.84		2.00 (1.47–2.52)	2.05 ± 0.69	
	PSQI						LAEP								
	Median (IQR)		Mean		p-Value		Median (IQR)		Mean		p-Value				
Levetiracetam N = 36	3.00 (2.00–4.00)		3.77 ± 2.48		0.401		31.00 (24.25–37.00)		32.38 ± 8.74		0.049				
Conventional N = 38	3.00 (1.00–5.00)		3.55 ± 2.77				26.50 (21.75–34.00)		28.39 ± 9.87						

IQR (interquartile range), BPAQ (Buss–Perry Aggression Questionnaire), DASS-21 (Depression, Anxiety, and Stress Scale 21), QOLIE-10 (patient-weighted Quality of life Index in Epilepsy), PSQI (Pittsburgh Sleep Quality Index), LAEP (Liverpool Adverse Events Profile).

Table 6
Comparison between biomarker levels and modules of MINI scale in subset of PWE using Mann-Whitney test.

Biomarkers	All patients		LEV		Conventional AEDs		p-Value between LEV and conventional AEDs (PBAE + ve events)	
	PBAE (+ve) (n = 36) (median, IQR)	PBAE (-ve) (n = 38) (median, IQR)	PBAE (+ve) (n = 23) (median, IQR)	p-Value	PBAE (-ve) (n = 13) (median, IQR)	PBAE (+ve) (n = 13) (median, IQR)	PBAE (-ve) (n = 25) (median, IQR)	p-Value
BDNF (pg/ml)	7.33 (4.67–9.44)	7.29 (4.70–8.68)	6.05 (4.62–9.39)	0.957	7.84 (4.66–8.31)	8.20 (6.37–10.18)	7.14 (4.82–9.19)	0.701
5-HIAA (ng/ml)	30 (21.98–44.87)	29.29 (23.17–39.67)	30 (20.96–52.75)	0.383	25 (14.23–48.07)	30 (27.69–43.20)	30 (26.28–37.56)	0.584
HVA (ng/ml)	7.76 (6.12–13.63)	7.74 (6.12–12.03)	8.57 (6.28–13.36)	0.538	7.71 (5.62–10.07)	7.51 (6.42–22.2)	7.75 (6.25–12.24)	0.963
TAC (units)	405.55 (286.58–463.72)	405.55 (289.05–463.72)	411.77 (265.27–515.27)	0.996	441.44 (360.44–528.11)	398.88 (348.11–434.11)	365 (240.00–436.77)	0.340

MINI (MINI International Neuropsychiatric Interview), PWE (person with epilepsy), LEV (levetiracetam), AEDs (antiepileptic drugs), PBAE + ve. at least one type of psychiatric and behavioral adverse effects present as per MINI modules, PBAE – ve. none of psychiatric and behavioral adverse effects present as per MINI modules, BDNF (brain-derived neurotrophic factor), 5-HIAA (5-hydroxyindoleacetic acid), HVA (homovanillic acid), TAC (total antioxidant capacity in $\mu\text{mol Trolox} \text{equiv./L}$).

the AE if any occurring due to AEDs adds on to the causation of poor compliance [25]. Pharmacoeconomic studies have generally considered the cost of treatment for the disease conditions; however, a study estimated the cost of side effects during AEDs treatment, i.e., healthcare resources used for the side effect management [26]. According to this study, cost due to behavioral side effects was the 2nd highest and contributed a major proportion of the total cost of treatment. A recent study concluded that out of 4085 PWE, who were newly started on AED treatment, 17.2% of PWE had PBAEs and 13.8% reported intolerability [10]. Similarly, another study done on 1394 PWE, who were on newer AEDs, reported that 16% of PWE experienced PBAEs. This study highlighted that significantly more PBAEs were accounted by LEV with an incidence rate of 15.7% ($p < 0.001$) as compared to lamotrigine, gabapentin, and oxcarbazepine [27]. A retrospective study in 2017 [5] comparing the PBAEs of conventional and newer AEDs has shown that LEV had highest PBAEs rates when compared to an aggregate of other AEDs ($p < 0.001$). In this study, PWE on LEV had significantly higher intolerability (17.7%), and these led to more dose reduction (9.4%) and complete discontinuation (8.3%) when compared to other AEDs ($p < 0.001$). This study also revealed that conventional AEDs like CBZ, PHT, and VPA were associated with lower PBAEs as compared to other AEDs including LEV.

In this study, comparison of BPAQ, DASS-21, QOLIE-10, PSQI, and LAEP scores was conducted in all PWE as well as in the subset of PWE where neuroendocrine status was assessed. As per PSQI scores, AEDs treatment was not associated with poor sleep quality (median PSQI scores: < 5 , in both groups); however, the conventional AEDs group had relatively better sleep quality than LEV group ($p = 0.040$). Previous studies showed that LEV can be considered as sleep-friendly AED as sleep was of better quality and restful with fewer awakenings [28,29]. Our study showed that among the subset of PWE, LEV group had significantly more physical aggression and anger than conventional AEDs according to BPAQ score. In a previous study, PWE in LEV group had more aggression problems (49%) than other AEDs (39%) and control (7%) [30]. The QOLIE-10 score between both groups was not significantly different, which is in accordance with the previous study that reported no difference in QOLIE-10 scores between newer and conventional AEDs [31].

As per LEAP score, AE associated with LEV and conventional AEDs has no significant difference in all PWE, though marginally higher LEAP scores (higher adverse effects) in LEV group were noted than conventional AEDs among the subset of PWE ($p = 0.049$). This result is in accordance with a randomized clinical trial carried out in 2012 [32], which reported no significant difference in LAEP scores between LEV and older AEDs.

The exact mechanism which is responsible for higher PBAEs with LEV is not known. Majority of drugs used to treat major depression, bipolar disorder, and psychotic disorders such as schizophrenia target monoamine (dopamine, serotonin, and noradrenaline) receptors, transporters involved in their reuptake, and metabolism [33]. It is reported that the serum BDNF level is lower in major depressive disorders [12,34] and psychotic disorders like schizophrenia [35]. Serum BDNF levels reported by previous studies range from 4.28 to 16.69 ng/ml in healthy control population [36–38] and from 9.8 to 13.9 ng/ml in patients with depression [38,39]. In our study, the serum BDNF levels were 7.33 (median, IQR: 4.67–9.44) ng/ml. The plasma level of homovanillic acid (HVA—the metabolite of dopamine) significantly decreased in patients with depression [13] and is elevated in acute psychotic states including psychotic relapses of schizophrenia [14,40]. Homovanillic acid levels reported by previous studies range from 6.8 to 8.7 ng/ml in healthy control [41,42], whereas patients with depression have HVA levels ranging from 4.5 to 13.8 ng/ml [39,43]. Our study found HVA levels as 7.76 (median, IQR: 6.12–13.63) ng/ml. Studies have reported higher plasma levels of 5-HIAA in patients with depression [13]. Level of 5-HIAA

Table 7
Correlations between BPAQ, DASS-21, QOLIE-10, PSQI, and LAEP scores among all PWE (n = 163).

Spearman's rho (correlation coefficient) (p value)	PA	VA	A	H	BPAQ	D	AN	S	DASS-21	QOLIE-10	PSQI	LAEP
PA	–	0.848 (<0.001)	0.903 (<0.001)	0.869 (<0.001)	0.939 (<0.001)	0.483 (<0.001)	0.533 (<0.001)	0.514 (<0.001)	0.517 (<0.001)	0.310 (<0.001)	0.250 (0.001)	0.238 (0.002)
VA	0.848 (<0.001)	–	0.884 (<0.001)	0.819 (<0.001)	0.926 (<0.001)	0.468 (<0.001)	0.514 (<0.001)	0.512 (<0.001)	0.511 (<0.001)	0.257 (0.001)	0.243 (0.002)	0.211 (0.007)
A	0.903 (<0.001)	0.884 (<0.001)	–	0.879 (<0.001)	0.965 (<0.001)	0.531 (<0.001)	0.563 (<0.001)	0.570 (<0.001)	0.569 (<0.001)	0.320 (<0.001)	0.220 (0.005)	0.273 (<0.001)
H	0.869 (<0.001)	0.819 (<0.001)	0.879 (<0.001)	–	0.939 (<0.001)	0.591 (<0.001)	0.605 (<0.001)	0.620 (<0.001)	0.615 (<0.001)	0.303 (<0.001)	0.176 (0.025)	0.235 (0.003)
BPAQ	0.939 (<0.001)	0.926 (<0.001)	0.965 (<0.001)	0.939 (<0.001)	–	0.542 (<0.001)	0.585 (<0.001)	0.583 (<0.001)	0.583 (<0.001)	0.583 (<0.001)	0.307 (0.003)	0.253 (0.001)
D	0.483 (<0.001)	0.468 (<0.001)	0.531 (<0.001)	0.591 (<0.001)	0.542 (<0.001)	–	0.845 (<0.001)	0.885 (<0.001)	0.945 (<0.001)	0.411 (<0.001)	0.283 (<0.001)	0.334 (<0.001)
AN	0.533 (<0.001)	0.514 (<0.001)	0.563 (<0.001)	0.605 (<0.001)	0.586 (<0.001)	0.845 (<0.001)	–	0.873 (<0.001)	0.950 (<0.001)	0.377 (<0.001)	0.337 (<0.001)	0.312 (<0.001)
S	0.514 (<0.001)	0.512 (<0.001)	0.570 (<0.001)	0.620 (<0.001)	0.585 (<0.001)	0.885 (<0.001)	0.873 (<0.001)	–	0.951 (<0.001)	0.423 (<0.001)	0.286 (<0.001)	0.333 (<0.001)
DASS-21	0.517 (<0.001)	0.511 (<0.001)	0.569 (<0.001)	0.615 (<0.001)	0.583 (<0.001)	0.945 (<0.001)	0.950 (<0.001)	0.951 (<0.001)	–	0.432 (<0.001)	0.343 (<0.001)	0.361 (<0.001)
QOLIE-10	0.310 (<0.001)	0.257 (0.001)	0.320 (<0.001)	0.303 (<0.001)	0.307 (<0.001)	0.411 (<0.001)	0.377 (<0.001)	0.423 (<0.001)	0.432 (<0.001)	–	0.488 (<0.001)	0.719 (<0.001)
PSQI	0.250 (0.001)	0.243 (0.002)	0.220 (0.005)	0.176 (0.025)	0.230 (0.003)	0.283 (<0.001)	0.337 (<0.001)	0.286 (<0.001)	0.343 (<0.001)	0.488 (<0.001)	–	0.479 (<0.001)
LAEP	0.238 (0.002)	0.211 (0.007)	0.273 (<0.001)	0.235 (0.003)	0.253 (0.001)	0.334 (<0.001)	0.312 (<0.001)	0.361 (<0.001)	0.361 (<0.001)	0.719 (<0.001)	0.479 (<0.001)	–

PA (physical aggression), VA (verbal aggression), A (anger), H (hostility), BPAQ (Buss–Perry Aggression Questionnaire), D (depression), AN (anxiety), S (stress), DASS-21 (Depression, Anxiety, and Stress Scale 21), QOLIE-10 (patient-weighted Quality of life Index in Epilepsy), PSQI (Pittsburgh Sleep Quality Index), LAEP (Liverpool Adverse Events Profile).

in our study was 30.0 (median, IQR: 21.98–44.87) ng/ml and that reported from previous studies range from 9.8 to 80.87 ng/ml [44]. Oxidative stress is believed to cause neurodegeneration leading to epilepsy and cognitive decline [45]. With the multiplicity of antioxidant pathways, total antioxidant power measurement in serum or plasma may show the overall influences of drug treatment, lifestyle, and nutritional supplements on an individual's antioxidant capacity [46]. Previous study reported TAC levels in the healthy controls as $675 \pm 61 \mu\text{mol Trolox}^{\circledR} \text{equiv./L}$ [47], and levels in our study were 405.55 (median, IQR: 286.58–463.72) $\mu\text{mol Trolox}^{\circledR} \text{equiv./L}$.

5. Conclusion

Chronic administration of AEDs is a necessity to have proper control of seizure in PWE, but simultaneously, the PBAEs associated with AEDs administration lead to significant compliance issues. Though several studies have pointed out that there is occurrence of PBAEs with AEDs administration, there is lack of derivation of any specific mechanism behind this, which can aid in optimizing AEDs treatment. To the best of our knowledge, this is the first study to assess and compare neuroendocrine markers levels and their relationship with PBAEs in PWE on LEV and conventional AEDs. Our study found higher PBAEs and more AE in the LEV group as compared to conventional AEDs. However, there was no significant difference in neuroendocrine biomarker levels when compared among PWE with presence and absence of PBAEs or between LEV and conventional AEDs. This fact highlights that the higher association of PBAEs in the LEV group may have other putative mechanisms rather than the studied biomarkers, i.e., BDNF, HVA, 5-HIAA, and TAC. The major limitation of our study was its cross-sectional study design and small sample size. There is a need for a prospective study with a larger number of subjects and long duration of follow-up to observe the complete AE profile and its causation.

Declaration of Competing Interest

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