Adverse effect profiling of persons with epilepsy in a tertiary care centre using LAEP scale: Correlation with co-morbid depression.

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Abstract

Purpose: Anti-seizure medications (ASMs) are associated with a variety of adverse events (AEs) that have a significant detrimental impact on quality of life and treatment adherence. The aim of the study was to identify and quantify the AEs of ASMs in persons with epilepsy (PWE) using Liverpool Adverse Events Profile (LAEP), and to determine the feasibility of LAEP for predicting depression in PWE. Methods: After ethical clearance, 309 PWE above 18 years of age, on ASMs, attending epilepsy clinic in neurology outpatient department of All India Institute of Medical Sciences, New Delhi, India, were recruited and evaluated for depression using different assessment tools, and LAEP screening tool was used for adverse event profiling. Results: The mean LAEP scores in PWE were 28.2±6.2 and ranged from 19 to 49. Only 16 PWE had LAEP score [?]45 i.e. had high toxicity. Phenytoin had the highest LEAP score, followed by carbamazepine, levetiracetam, and sodium valproate. As compared to monotherapy, PWE on polytherapy had higher LAEP score (26.7+-5.9 vs. 29.03+-6.3; p=0.0013). Subjects positive for depression had significantly higher LAEP score than PWE without depression (33.5+-6.2 vs. 24.7+-3.1; p<0.0001). A strong positive correlation of the LAEP score was observed with depression scores as assessed by different assessment tools, and a LAEP score of [?]28 was recommended to screen PWE for depression. Conclusion: The systematic use of LAEP in epilepsy outpatient settings will allow for better detection and management of ASM's adverse effects, as well as the identification of PWE at risk of depression.

Adverse effect profiling of persons with epilepsy in a tertiary care centre using LAEP scale: Correlation with co-morbid depression.

Running Title: Adverse effect profiling of persons with epilepsy on ant-seizure medications

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Methods: After ethical clearance, 309 PWE above 18 years of age, on ASMs, attending epilepsy clinic in neurology outpatient department of All India Institute of Medical Sciences, New Delhi, India, were recruited and evaluated for depression using different assessment tools, and LAEP screening tool was used for adverse event profiling.

Results: The mean LAEP scores in PWE were 28.2±6.2 and ranged from 19 to 49. Only 16 PWE had LAEP score [?]45 i.e. had high toxicity. Phenytoin had the highest LEAP score, followed by carbamazepine, levetiracetam, and sodium valproate. As compared to monotherapy, PWE on polytherapy had higher LAEP score (26.7+-5.9 vs. 29.03+-6.3; p=0.0013). Subjects positive for depression had significantly higher LAEP score than PWE without depression (33.5+-6.2 vs. 24.7+-3.1; p<0.0001). A strong positive correlation of the LAEP score was observed with depression scores as assessed by different assessment tools, and a LAEP score of [?]28 was recommended to screen PWE for depression.

Conclusion: The systematic use of LAEP in epilepsy outpatient settings will allow for better detection and management of ASM's adverse effects, as well as the identification of PWE at risk of depression.

Keywords: Persons with epilepsy (PWE), Depression, Liverpool Adverse Events Profile (LAEP), Anti-seizure medications (ASMs), Adverse events (AEs)

Key points:

1. The routine use of LAEP in epilepsy clinics may enhance identification and quantification of adverse effects, and will also help in recognizing persons with epilepsy who are more likely to become depressed, and can be referred for psychiatric evaluation and management.
2. The most common adverse events were feeling of anger/ aggression (92.9%), nervousness and/or agitation (72.7%), memory problems (67.6%), tiredness (62.5%), headache (54.7%), restlessness (43.6%), hair loss (43.4%), depression (43%) and disturbed sleep (39.2%)
3. Persons with epilepsy on polytherapy, and those who were positive for depression had higher LAEP score.
4. At a cut-off of [?] 28, LAEP can screen persons with epilepsy positive for co-morbid depression as well as monitor the AEs of ASMs.

Introduction

Anti-seizure medications (ASMs) are the mainstay of management of epilepsy [1,2]. However, data from cross-sectional studies and randomized controlled trials have revealed that up to 80% of persons with epilepsy (PWE) taking ASMs experience an adverse effect [3], the most common being gastrointestinal disturbances, loss of appetite and nausea, weight gain, tremor, rash and fatigue/tiredness [4]. Even though these adverse effects (AEs) adversely impact health related quality of life and reduces patient compliance [1,3,5], it has been observed that clinicians either under-report or sometimes overlook them [6]. Since routine screening for AEs in PWE may improve patients' health related quality of life, need of a screening tool that can reliably identify and detect the nature and frequency of AE in PWE on ASMs and also is easy to administer in a busy clinical setting was identified and the Liverpool Adverse Events Profile (LAEP) was developed in the 1990s by Baker et al. to evaluate the most common negative AEs encountered by the patients that impact patient compliance to prescribed ASMs [7–12]. LAEP is a validated, epilepsy specific, 19-item questionnaire which assesses the physical, psychological and cognitive state of PWE [13] and is one of the widely used scales to detect and quantify the presence and severity of AEs associated with different ASMs [7,14,15]. Besides the AEs with ASMs, now it is amply clear that there are multiple co-morbidities associated with epilepsy in PWE which require identification and intervention. Depression is one such pathology with prevalence up to

40%, and PWE need to be evaluated routinely [16]. In this study, using LAEP the adverse effects of ASMs in PWE were identified and quantified and in order to assess the feasibility of using LAEP score for predicting depression in PWE, the correlation with different assessment tools for depression was determined.

1. **Material and Methods**
2. **Study design:** A prospective observational study
3. **Study Participants:** After the Institute Ethics Committee approval, PWE attending neurology outpatient department (OPD) at All India Institute of Medical Sciences (AIIMS), New Delhi, India were included in the study. The inclusion criteria for recruiting the patients were age [?] 18years, either gender, meet diagnostic criteria for epilepsy as per ILAE, and on ASMs. Written informed consent was obtained; patient and treatment details relevant to the study were recorded.
4. **Assessment of adverse effects experienced by PWE:** LAEP screening tool was used for adverse event profiling in enrolled PWE. LAEP contains 19 items related to both physical and psychological symptoms. Each item is assessed on a 4-point likert scale where [1] = never, [2] = seldom, [3] = sometimes and [4] = often or always, and scores can range from 19 to 76. Higher scores indicate higher levels of prevalence and severity of adverse effects. A cut-off point of [?]45 on the LAEP indicates "high toxicity" whereas <45 indicates "low toxicity" i.e. mild to moderate adverse effects [3,17,18]. In this study, the participants were asked all the 19 questions, and their responses were recorded.
5. **Assessment of depression in PWE:** The instruments used for the detection of depression in PWE were MINI, NDDI-E, HPHQ-9 and HAM-D. Permission for using all above tools, where required was duly taken.
6. **Correlation between LAEP scores and depression in PWE:**Since LAEP contains items pertaining to emotional and psychosomatic symptoms related to depression, association of the total LEAP score with co-morbid depression in PWE using other assessment tools was determined.
7. **Statistical analysis:** Statistical analysis was performed using STATA statistical software, version 14. The sensitivity, specificity, likelihood ratio positive and negative, and area under the curve (AUC) for the ROC curve with its 95% confidence intervals (CIs) were calculated using MINI as reference standard. The categorical variables between the group with depression and the group without depression were compared using the chi-square or the exact Fisher test, while continuous variables were compared using the Student's t test or Mann–Whitney U test. Logistic regression model was applied to determine the influence of demographic, epilepsy, and ASM-related factors on LAEP results. Correlation analysis was also performed between the LAEP score, and depression scores of other tools. A significance level of $p < 0.05$ (two-tailed) was adopted.
8. **Results**
9. **Liverpool Adverse Events Profile and clinico-demographic characteristics:** Three hundred and nine PWE (51.5% females) attending the neurology OPD at AIIMS, New Delhi between July 2018 – March 2020, meeting eligibility criteria were enrolled in the study, and underwent neuropsychiatric evaluation. The age of the participants ranged from 18–75 years, mean age 28.8+-9.1 years. Two hundred and nine PWE had a diagnosis of generalized seizures and 100 PWE had focal seizures. A total of 236 subjects had had seizures within 2 years and 73 subjects were seizure free [?] 2 years (Table 1).

Among the PWE, 38.2% were on monotherapy and rest were on polytherapy. Among monotherapy, most PWE were on Levetiracetam (62 out of 118). Clobazam was the most commonly used ASM in polytherapy (153 out of 191) followed by levetiracetam (115 out of 191). In polytherapy, while 89 PWE received two ASMs, 59 received three ASMs, 35 received four ASMs, 07 received five ASMS, and 01 PWE received seven ASMs. Table 2 gives the mean score, medians, and frequency response of each item of the LAEP. The mean LAEP scores in PWE were 28.2 +- 6.2 and ranged from 19 to 49. There was no significant difference in LAEP scores based on demographic variables. Expectedly, the exceptions were number of ASMs as polytherapy was more likely to be related with higher LAEP scores (Table 1).

Adverse event profiling using LAEP: The most common AE were feeling of anger/ aggression (92.9%), nervousness and/or agitation (72.7%), memory problems (67.6%), tiredness (62.5%), headache (54.7%),

restlessness (43.6%), hair loss (43.4%), depression (43%) and disturbed sleep (39.2%) (Figure 1). Only 16 PWE (5PWE on monotherapy and 11 on Polytherapy) had LAEP score [?] 45 i.e. had high toxicity.

ASMs and LAEP scores: The frequency of common AEs varied among different ASMs. Feeling of anger/ aggression was more present in CBZ> LEV> SV> PHT, nervousness and/or agitation in CBZ> SV> LEV> PHT, memory problems in PHT> CBZ> LEV> SV, tiredness in LEV> PHT> CBZ> SV, depression in PHT> CBZ> LEV> SV, headache in PHT> LEV> CBZ> PHT, hair loss in LEV=CBZ> SV> PHT, and disturbed sleep in PHT> CBZ> SV> LEV. However, LEV polytherapy was significantly associated with three AEs - tiredness (p=0.007), difficulty in concentrating (p=0.008), and depression (p=0.043).

Per se phenytoin was associated with highest LEAP score (n= 6, 28.7 +- 9.8), followed by carbamazepine (n=17, 27.8 +- 5.3), levetiracetam (n=62, 26.7 +- 5.8), and sodium valproate (n=27, 25.8 +- 5.3), but the difference was not statistically significant. In addition, there was no significant difference in LAEP score when the daily dose range of prescribed ASMs was compared (carbamazepine - <800mg vs. [?]800mg, 27.8+- 6.9 vs. 23+-0; phenytoin- 100mg vs. >100mg, 25+- 1.7 vs. 32.3 +- 14.01; sodium valproate- <1000mg vs. [?] 1000mg, 26.1 +- 6.03 vs. 25.1 +- 3.8), except in case of levetiracetam where PWE on [?]1500mg had higher LAEP score than PWE on <1500mg (p= 0.0525) (Table 3). In Levetiracetam group on [?]1500mg, there were significantly increased complaints of adverse events i.e. difficulty in concentrating (p= 0.0097), dizziness (p= 0.0478), and depression (p= 0.0116). Polytherapy was associated with higher LAEP score as compared to monotherapy and the difference was statistically significant (p=0.0013) (Table 1). There was a statistically significant difference between PWE on monotherapy or polytherapy for certain specific items on LAEP namely headache (p= 0.045), shaky hands (p= 0.003) and memory problems (p= 0.000), where as adverse events related to mood and behaviour were restlessness (p=0.043), feeling of anger and aggression to others (p=0.036), nervousness or agitation (p=0.002) and depression (p= 0.000) (Table 4). In polytherapy combinations, the most commonly prescribed ASMs were levetiracetam and clobazam. The LAEP score increased with addition of an ASM, and was higher when either of the ASMs levetiracetam, carbamazepine, phenytoin and sodium valproate were prescribed with three or more ASMs (Table 5).

Prevalence of depression in PWE: Using the different tools, the percentage of PWE detected positive for depression were 38.8, 39.8, 43 and 43.4 with MINI, NDDI-E, HAM-D and PHQ-9 respectively. In case of LAEP, as per the 17th item of scale i.e. depression, 57% reported no depression, 22.3% rarely had depression, 17.2% experienced it sometimes, and 3.6% always or often reported depression. PWE with depression had significantly (p<0.0001) higher LAEP score than PWE without depression (Table 1).

ROC curve for detecting depression in PWE: The frequency of responses of each item of LAEP is given in table 2. ROC analysis revealed that at a cut-off score of [?]28, the LAEP had a sensitivity of 88.33%, a specificity of 83.60%, and an area under the curve (AUC) of 0.932 (95% confidence interval [CI] = 0.905–0.959; standard error [SE] = 0.014) (Table 6, Figure 2).

All the adverse events in LAEP had significant association with depression irrespective of nature i.e. whether adverse events were related to CNS (neurological) or non-CNS (cosmetic or gastrointestinal) or psychiatric (mood and behaviour).

Correlations between LAEP and depression scores: A statistically significant, strong positive correlation of LAEP score with depression scores as assessed by different screening instruments was observed (Table 7). Subjects with higher LAEP score had more severe depression.

Discussion:

Upto 88 percent of PWE using ASMs have at least one AE, which has a significant detrimental impact on their quality of life and treatment adherence, resulting in treatment failure and seizure recurrence [1,10,19]. It is apparent that early detection of PWE at high risk of adverse event burden might help avoid treatment failures. Apart from this, psychiatric co-morbidities can potentially have a negative influence on seizure control [20]. It is evident that the treatment of epilepsy cannot be limited to the achievement of seizure-freedom alone, managing related co-morbidities particularly depression is important [21]. While clinicians

can use any depression assessment instrument, such as the MINI, NDDI-E, HAM-D, or PHQ-9 to identify psychiatric co-morbidities, it may not be feasible for an epileptologist/ neurologist to routinely evaluate each and every PWE for depression and ASM related AEs using different tools. A quick inventory that can screen PWE at risk of depression as well as the AEs of ASMs without unnecessarily increasing the burden to clinicians may be useful and save time and resources. The LAEP is a commonly used screening tool that quantifies subjective symptoms reported by patients. According to many studies, LAEP screens a greater percentage of adverse events than spontaneous reporting [11,17,22]. According to Carreno et al (2008), ASM-related AE was found in 34% of PWE when assessed by spontaneous reporting and 66% when assessed using a checklist [22]. Another study reported that the prevalence of adverse events identified by a validated screening approach was nearly three times that of an unstructured interview [11,23]. Thus LAEP score needs to be obtained for assessing prevalence of AEs in PWE. In earlier studies, a wide variation in mean LAEP scores in PWE on ASMs has been reported, ranging from 27 to 43 [24]. In this study, a comparatively lower mean LAEP score was observed i.e. 28.15+-6.24, inspite of the fact that study was carried out in a tertiary care setting. The reason for lower score in this study is not clear. Interestingly, LAEP scores were also not found to be influenced by demographic variables like gender, age, seizure control, and epilepsy type. In many studies LAEP score increased with female gender, older age, higher seizure frequency, uncontrolled generalized seizures, etc [1,14,19]. In case of ASMs, PWE on carbamazepine were reported to have the highest LAEP score in some studies [13], however in this study, phenytoin use was associated with the highest LAEP score followed by Carbamazepine. A recent study has also reported that PWE using oxcarbazepine had a higher score of LAEP [14]. Kowski et al (2016) reported significant association of levetiracetam with anger/aggression, nervousness/agitation, and depression [19]. In our study, LEV polytherapy was significantly associated with tiredness, difficulty in concentrating, and depression. Feeling of anger/ aggression and nervousness and/or agitation were reported more with CBZ; depression, headache, disturbed sleep, and memory problems were more frequent in PHT; tiredness in LEV, and hair loss both in LEV and CBZ. While other studies have also reported that the incidence rate of AEs increase, with increased dosages of ASMs [25]. However, there was no significant difference in LAEP score when the daily dose range of prescribed ASMs was compared except in levetiracetam where PWE on [?]1500mg had higher LAEP score than PWE on <1500mg. Levetiracetam [?]1500mg group was significantly associated with adverse events i.e. difficulty in concentrating, dizziness, and depression. Higher seizure frequency, symptomatic epilepsy, drug resistance, ASM polytherapy, younger age at epilepsy onset, female gender, and depression are all shown to be related with a higher burden of AEs of ASM [1,14,19]. The current study found that PWE on polytherapy and those having depression had significantly higher LAEP score, however no significant association was observed with gender, age, seizure control and type of seizures. Our observation that polytherapy causes more adverse effects than monotherapy was consistent with the results documented by previous studies [13,26]. Andrew et al (2012) reported that tiredness, memory problems and difficulty concentrating were the most common AEs and were consistently higher in polytherapy than in monotherapy [13]. It has been observed that ASMs have a 30-40% incidence of adverse side effects, and this rate increases to 50-60% if PWE takes two or more drugs at the same time [27,28]. A consistently higher score of LAEP was reported in PWE with depression. Mula (2009) has also reported that as compared to PWE without depression, PWE with depression are more likely to experience adverse effects of ASMs [29]. Some studies have reported positive correlation of the total LEAP score with depression [15]. This is presumed to be because the LAEP contains items pertaining to emotional and psychosomatic symptoms related to depression, and it is suggested that LAEP may be useful for screening major depression [15,30]. However, these workers contended that the use of the LAEP scale along with depression assessment tool may be necessary due to the fact that some AEs of ASMs are readily assessed through routine screening (rash, weight gain/loss), others are difficult to observe, and some of the AEs of ASMs resemble with somatic symptoms of depression such as difficulty in concentrating, fatigue and sleep disorders [15,18]. We validated LAEP using MINI as reference standard, and it was seen that at a cut-off of [?] 28 LAEP can screen PWE positive for co-morbid depression as well as monitor the AEs of ASMs. Kwon & Park (2018) suggested a cut-off of >40 (sensitivity 80%; specificity 80%) could detect major depression disorder [15]. However, with a cut-off of [?] 28 (sensitivity 88.3%; specificity 83.6%) of LAEP, even minimal or mild depression will not

be overlooked. It is suggested that PWE with a LAEP score of more than 28 be referred for psychiatric evaluation and subsequent investigation with diagnostic tools of depression such as MINI, SCID, etc. The limitation of the study was its cross-sectional design. This study was carried out in a tertiary care center, where the majority of the patients have refractory or drug resistant epilepsy and therefore, the results might not be representative of PWE in the general population.

Conclusion:

The systematic use of LAEP in epilepsy clinics may enhance identification and quantification of ASM adverse effects, as well as lead prescription adjustments to decrease toxicity or adverse effects, and improve patients' health status. Use of LAEP will also help in recognizing PWE who are more likely to become depressed, and thus can be referred to psychiatry for further clinical assessment and management.

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Figure legends:

Figure 1: Percentage and severity of common adverse effects measured by Liverpool Adverse Events Profile (LAEP). Note: 1, never a problem; 2, rarely a problem; 3, sometimes a problem; and 4, always a problem

Figure 2: Receiver operator characteristic (ROC) curve of the LAEP for detecting depression in PWE.

Table 1: Characteristics of enrolled PWE and their LAEP score.

Variables	Variables	LAEP Score	p value
Total PWE = 309	**Total PWE = 309**	28.2 ± 6.2	
Age	Age 18-30 years (n=207)	27.9 ± 5.9	0.428
	Age > 30 years (n=102)	28.5 ± 6.9	
Gender	Male (n=150)	27.9 ± 6.2	0.483
	Female (n=159)	28.4 ± 6.3	
Epilepsy Type	Focal (n= 100)	27.6 ± 5.7	0.294
	Generalized (n=209)	28.4 ± 6.5	
Number of ASMs	Monotherapy (n=118)	26.7 ± 5.9	**0.0013**
	Polytherapy (n=191)	29.03 ± 6.3	
Seizure Control	Seizures free [?] 2yrs (n=73)	28.3 ± 7.5	0.811
	Seizures within 2yrs (n=236)	28.1 ± 5.8	
Depression status	Depression (n= 120)	33.5 ± 6.2	**<0.0001**
	Without Depression (n= 189)	24.7 ± 3.1	

Table 2: The mean score, medians, and frequency response of each item of the LAEP (n= 309)

Symptoms	LAEP items	Median (range)	N
Mood and behavior (Psychiatric symptoms)	**Depression**	1 (1-4)	1
	Restlessness	1 (1-4)	1
	Feelings of anger & aggression to others	3 (1-4)	2
	Nervousness or agitation	2 (1-4)	7
Cosmetic			
(Non-CNS symptoms)	**Hair loss**	1 (1-4)	1
	Problems with Skin (e.g. achne or rash)	1 (1-4)	2
Gastrointestinal			
(Non-CNS symptoms)	**Upset stomach**	1 (1-4)	2
	Weight gain	1 (1-4)	2
	Trouble with mouth or gums	1 (1-4)	3
Neurological			
(CNS related symptoms)	**Difficulty in concentrating**	1 (1-4)	2

	Double or blurred vision	1 (1-4)	2
	Headache	2 (1-4)	1
	Shaky hands	1 (1-4)	2
	Unsteadiness	1 (1-4)	2
	Tiredness	2 (1-4)	1
	Dizziness	1 (1-4)	2
	Sleepiness	1 (1-4)	2
	Memory problems	2 (1-4)	1
	Disturbed sleep	1 (1-4)	1
Overall Score	**Overall Score**	27 (19-49)	

Table 3: Antiseizure medication ranges and significant differences in LAEP items between medications

	Ta
	Le
Number of PWE	62
Dose range	<1
N	28
LAEP item	**LA**
Overall Score	25.
Unsteadiness	1.0
Tiredness	1.6
Restlessness	1.3
Feelings of anger & aggression to others	2.2
Nervousness or agitation	1.6
Headache	1.5
Hair loss	1.7
Problems with Skin (e.g. achne or rash)	1.1
Double or blurred vision	1.1
Upset stomach	1.0
Difficulty in concentrating	**1.0**
Trouble with mouth or gums	1.0
Shaky hands	1.1
Weight gain	1.1
Dizziness	**1.0**
Sleepiness	1.2
Depression	**1.2**
Memory problems	1.5
Disturbed sleep	1.3
Note: *p<0.05, **p<0.01	**No**

Table 4: Frequency of adverse events in enrolled PWE on monotherapy and polytherapy

LAEP scale items	**LAEP scale items**	**Monotherapy**
		N
Unsteadiness	**Present**	**10**
	Absent	**108**
Tiredness	**Present**	**66**
	Absent	**52**
Restlessness	**Present**	**43**
	Absent	**75**

Feelings of anger & aggression to others	**Present**	**105**
	Absent	**13**
Nervousness or agitation	**Present**	**78**
	Absent	**40**
Headache	**Present**	**56**
	Absent	**62**
Hair loss	**Present**	**51**
	Absent	**67**
Problems with Skin (e.g. achne or rash)	**Present**	**7**
	Absent	**111**
Double or blurred vision	**Present**	**12**
	Absent	**106**
Upset stomach	**Present**	**19**
	Absent	**99**
Difficulty in concentrating	**Present**	**24**
	Absent	**94**
Trouble with mouth or gums	**Present**	**3**
	Absent	**115**
Shaky hands	**Present**	**22**
	Absent	**96**
Weight gain	**Present**	**14**
	Absent	**104**
Dizziness	**Present**	**15**
	Absent	**103**
Sleepiness	**Present**	**31**
	Absent	**87**
Depression	**Present**	**35**
	Absent	**83**
Memory problems	**Present**	**65**
	Absent	**53**
Disturbed sleep	**Present**	**39**
	Absent	**79**
***p<0.05, **p<0.01, ***p<0.001	***p<0.05, **p<0.01, ***p<0.001	***p<0.05, **p<0.01, ***p<0.00

Table 5: Prescription of anti-seizure medications in monotherapy and polytherapy and their LAEP score

	Monotherapy	**Drug Combinations + 1 ASM**	**Drug Combinations + 2 ASM**	**Drug Combinations + 3 ASM**	**Dru + 4**
ASM	Levetiracetam (LEV)				
LAEP score	**26.7 ± 5.8**	**29.4 ± 7.4**	**28.5 ± 5.3**	**29.4 ± 6.8**	**26.**
N	62	39	41	27	7
ASM	Carbamazepine (CBZ)				
LAEP score	**27.8 ± 6.9**	**28.2 ± 6.6**	**30.3 ± 4.8**	**30.9 ± 7.2**	**27**
N	17	18	16	10	3
ASM	Phenytoin (PHT)				
LAEP score	**28.7 ± 9.8**	**30.8 ± 3.8**	**29 ± 5.5**	**31.4 ±8.6**	**26**
N	6	8	5	5	3
ASM	Sodium Valproate (SV)				
LAEP score	**25.8 ± 5.3**	**26.8 ± 5.6**	**29.5 ± 6.9**	**29.6 ± 6.1**	**25.**
N	27	19	21	18	5

ASM	Clobazam (CLB)				
LAEP score	**24 ± 0**	**29.1 ± 6.8**	**28.9 ± 5.7**	**28.9 ± 6.4**	**27.**
N	2	67	47	32	6
ASM	Lacosamide (LCM)				
LAEP score	**25 ± 0**	**37 ± 9.2**	**29.1 ± 5.3**	**30.1 ± 6.4**	**27.**
N	1	3	7	9	3
ASM	Lamotrigine (LMT)				
LAEP score	**24 ± 0**	**33.3 ± 9.4**	**28.4 ± 7.2**	**26.8 ± 5.3**	
N	1	7	11	8	
ASM	Oxcarbamazepine (OXC)				
LAEP score	**29 ± 4.2**	**29.4 ± 5.5**	**26.1 ± 2.7**	**28.1 ± 5.3**	
N	2	11	13	9	

Table 6: ROC and diagnostic efficiency statistics of LAEP for screening of depression in PWE, based on the MINI

Cut-point
[?] 26
[?] 27
[?] 28
[?] 29
[?] 30

AUC: area under curve; SE: standard error; LR+: positive likelihood ratio; LR-: negative likelihood ratio; SE: Standard err

Table 7: Correlations between MINI (suicidality), NDDI-E, HAM-D, PHQ-9, and LAEP scores among all PWE (n= 309).

Correlation Coefficient (p value)	LAEP score	MINI (Suicidality)	NDDI-E score	HAM-D score	PHQ-9 score
LAEP score	1.0000				
MINI (Suicidality)	**0.1347** (<0.05)	1.0000			
NDDI-E score	**0.7550** (<0.001)	**0.1930** (<0.001)	1.0000		
HAM-D score	**0.7940** (<0.001)	**0.1572** (<0.01)	**0.8201** (<0.001)	1.0000	
PHQ-9 score	**0.7351** (<0.001)	**0.670** (<0.01)	**0.8719** (<0.001)	**0.8257** (<0.001)	1.0000