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Original article

Depression in patients receiving pharmacotherapy for epilepsy: An audit in a tertiary care centre

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ABSTRACT

Background: The association of depression and epilepsy is thought to be bidirectional. The present study aimed to evaluate the prevalence of depression in patients on antiepileptic drugs (AEDs) and factors affecting it.
Methods: In this preliminary cross sectional study, patients at epilepsy clinic of a tertiary care centre were studied for occurrence of depression, using Hospital Anxiety and Depression Scale (HADS-D) and Patient Health Questionnaire (PHQ-2) scales. Correlation analysis was carried out to determine the factors associated with presence of depression in these patients.
Results: A total of 12 AEDs (maximum 5 per patient including older and newer) were prescribed to 933 patients in different treatment regimens over a period of 3 years. The median age of the patients was 22 years (10–77) and among them 63.5% were men. Mild and clinically relevant depression occurred in 279 (29.9%) and 223 (23.9%) patients, respectively. Mean HADS-D and PHQ-2 score was significantly higher with polytherapy as compared to monotherapy ($p < 0.001$). Patients on levetiracetam exhibited significantly higher HADS-D score in comparison to phenytoin ($p < 0.001$), carbamazepine ($p < 0.001$) and sodium valproate ($p < 0.05$). However, there was no significant difference in PHQ score among patients on monotherapy of different AEDs. Multivariate regression analysis suggested correlation between depression and seizure frequency, total number of AEDs and their load ($p < 0.001$).
Conclusion: Depressive symptoms were found to be present in more than half of the patients with epilepsy which require detailed work up for depression. Levetiracetam was found to be associated with a higher incidence of subclinical depression which needs further investigation.

Introduction

Epilepsy is a common chronic neurological disorder with prevalence rate varying from 4 to 6 per 1,000 persons in India [1]. Further, patients with epilepsy (PWE) are generally on multiple antiepileptic drugs (AEDs) which are often associated with behavioural alterations including depression and suicidal ideation [2]. The incidence of depression in patients with epilepsy ranges from 20 to 54% [3] which is a cause of concern and is often overlooked or under-recognized. The newer AEDs differ in their mechanism of action from the older agents and also have effect on cognition and mood. There are few reports of suicidal ideation also [4], nevertheless available evidence is insufficient to prove this association. However, risks associated with uncontrolled epilepsy outweigh the risk of behavioral alterations with AEDs.

The psychiatric adverse effects of AEDs are less frequently reported in non epileptic populations which may be due to lower doses of AEDs or due to underlying neurological condition, *per se* [5]. Epilepsy itself is known to be associated with depression with shared pathology and four to five time greater incidence [6,7]. Some studies have evaluated the relation between them by using various depression scales [2,8]. However, there is scarcity of literature regarding the prevalence of depression in PWE in Indian population [9]. Furthermore, these symptoms are sometimes used to be neglected in the routine follow up for the treatment of severe seizures in epilepsy.

Thus, the present study was done to evaluate the association of depression between use of AEDs (as an adverse effect), disease process (as estimated by seizure control) and other contributing factors in PWE. Depression was assessed by using Hospital Anxiety and Depression Scale-depression (HADS-D) and Patient Health Questionnaire-2 (PHQ-2). These two tests are recommended for rapid and proficient screening of depressive symptoms in PWE during routine clinical practice [10,11]. These both scales are

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validated in both adolescents and adults [12–14]. Moreover, this is a preliminary study to evaluate the depression like symptoms in PWE. Further, the comparison between newer and older AEDs was done to evaluate the difference, if any, in terms of occurrence of depression between two groups in Indian population.

The primary objective of the study was to determine the prevalence of depression in PWE on AEDs using HADS-D and PHQ-2 scales. The secondary objective was to determine the contributing factors such as age, gender, type of seizure, seizure frequency, type of AEDs, number of prescribed AEDs, their regimens, AED load, duration of treatment etc, responsible for depression in patients with epilepsy.

Methods

Study population

This was a preliminary cross-sectional observational study. Patients (age $\geq$ 10 years) diagnosed with epilepsy as per criteria of International League Against Epilepsy (ILAE) 2010 classification [15] and taking AEDs (either monotherapy or polytherapy) were recruited from the Epilepsy Clinic of outpatient department of All India Institute of Medical Sciences (AIIMS), New Delhi, India. Patients were divided into five groups on the basis of newer and older AEDs, (1) monotherapy with older AEDs; (2) monotherapy with newer AEDs; (3) combination of older AEDs; (4) combination of older and newer AEDs; (5) combination of newer AEDs. Newer AEDs included levetiracetam (LEV), lamotrigine (LTG), oxcarbazepine (OXC), zonisamide (ZNS), topiramate (TPM), and lacosamide (LCM). Older AEDs were phenobarbital (PB), phenytoin (PHT), carbamazepine (CBZ), sodium valproate (VPA), clobazam (CLB) and clonazepam (CLZ). The study conformed to Good Clinical Practice guidelines and was done under the guidelines of Declaration of Helsinki. The patients were enrolled after taking written informed consent. The study protocol was reviewed and approved by the Institute Ethics Committee, AIIMS, New Delhi (Ref No.: IESC/T-245/2010).

The effectiveness of AEDs in terms of seizure frequency was classified into four categories based on occurrence of seizure since last change in treatment regimen [16]. Category 1: seizure free, with no seizure in last 12 months (after starting treatment) and remained so throughout follow-up; category 2 included patients with at least one seizure in 6 months. Patients in category 3 had at least one seizure in a month. Patients in category 4 never became seizure-free or had at least one seizure in a week. Patients in category 3 and 4 had poor control of seizures while categories 1 and 2 exhibited good control of seizures. Baseline demographic data including gender, age, age at seizure onset, type(s) and frequency of seizures, epilepsy characteristics according to ILAE [15], details of current AED regimens (including dosages) and concomitant medications were collected.

AED load [prescribed daily dose (PDD)/defined daily dose (DDD)]

AED load for each patient was calculated as a sum of the ratio of PDD/DDD for each AED prescribed in the treatment regimen, where DDD corresponds to the assumed average maintenance daily dose of a drug for its main indication (WHO, 2013) [17]. AED load reflects the total burden (dose) of the AEDs on an individual PWE. It is calculated to evaluate the effect of polytherapy on overall dose of AEDs. Comparison of mean AED load of each patient on different treatment regimens of antiepileptic drugs was also done. It is a validated method to calculate the per person load of AEDs [18].

Assessment of depression

Hospital Anxiety and depression scale-depression (HADS-D) is a validated and standardized questionnaire that is used for assessment of depression in PWE based on their experience in last one week [19,20]. It is used to assess the presence and severity of depression in a non-psychiatric outpatient setting. HADS-D has 7 items based on a four-point Likert type scale: [0] = never, [1]; = sometimes [2], = most of the day [3], almost all day. The maximum score using this scale can be 21 points. Scores between 0–7 is considered as normal, 8–10 indicates mild depression and $\geq$11 corresponds to clinically relevant depression. HADS at a cut point of 7 had the best overall balance of sensitivity and specificity [13].

Similarly, Patient Health Questionnaire-2 (PHQ-2) is a tool to assess the occurrence of depressed mood and anhedonia in the past week. The purpose of this scale is to screen the patient for depression as a "first step" approach and not to establish a final diagnosis or to monitor the depression severity. PHQ-2 is a two-item measure validated by earlier researchers for use in primary health care [21]. The PHQ-2 score ranges from 0-6. The cutoff score of 3 has been used to maintain a balance sensitivity and specificity of the test [11,12].

Statistical analysis

Data were analyzed using SPSS (Statistical Package for Social Sciences – version 17 for Windows) software. Central tendency measures and percentages were used for the descriptive analysis of continuous and nominal variables, respectively. The comparison of qualitative data was done by using Chi-square test/Fisher's exact test; and for continuous data Student's t-test/Mann-Whitney U-test was applied, wherever applicable. Correlation between seizure control and HADS–D score was performed with Spearman analysis. Comparison between older and newer AEDs was done using Kruskal–Wallis one-way analysis of variance. Multivariate regression analysis was done to study the factors responsible for depression in PWE. The data was expressed as mean $\pm$ SD or median (range). A p-value less than 0.05 was considered as statistically significant.

Results

A total of 933 consecutive PWE were enrolled in the study. The median age of the patients was 22 ranging from 10 to 77 years. Almost 36% of the patients were female. The total of 12 AEDs (including both older and newer) were prescribed in different treatment regimens with up to a maximum of 5 AEDs per patient. There was almost equal distribution of PWEs on monotherapy, duotherapy and polytherapy. Number of patients receiving older AEDs was significantly more than those receiving newer AEDs, irrespective of the treatment regimen (monotherapy or polytherapy) (Table 1). The total number of patients getting only newer AEDs (either monotherapy or polytherapy) was significantly less than other three groups. Patients with generalized seizures were more than those with focal seizures. A demographic description of the study participants is provided in Table 1.

Effect on seizure outcome

Depending upon the frequency of occurrence of seizures, patients were divided into 4 categories. Patients having no seizure for last one year (category 1) were significantly higher as compared to patients with more than one seizure in a year (category 2, 3 and 4). The detail of seizure outcome of patients on monotherapy, duotherapy and polytherapy is presented in Table 2. Among patients participated in the study, more than 50% were having good

Table 1
Demographic characteristics of study participants (n = 993).

Parameters	N (%)
Gender (male, %)	592 (63.5)
Adolescents (10-18 yrs)	341 (36.5)
Adults (>18 yrs)	592 (63.5)
Age (years) at enrollment [Median (range)]	
Adolescents (10-18)	14 (10-18)
Adults (>18)	31 (18-77)
Age at onset of seizures (years)	
Median (range)	13 (0-75)
Seizure type	
Generalized onset	481 (51.6)
Focal onset	452 (48.4)
Number of antiepileptic drugs	
Monotherapy	316 (33.9)
Duotherapy	325 (34.8)
Polytherapy	292 (31.3)
Monotherapy of antiepileptic drugs (AEDs)	
Older AEDs	276 (29.6)
Newer AEDs	38 (4.1)
Polytherapy of antiepileptic drugs	
Older + older AEDs	275 (29.5)
Newer + newer AEDs	10 (1.1)
Older + newer AEDs	334 (35.8)
Antiepileptic drugs	
Phenytoin	253 (27.1)
Carbamazepine	293 (31.4)
Sodium valproate	412 (44.2)
Clobazam	369 (39.5)
Clonazepam	49 (5.3)
Phenobarbital	32 (3.4)
Levetiracetam	288 (30.9)
Lamotrigine	88 (9.4)
Oxcarbazepine	78 (8.4)
Topiramate	35 (3.8)
Zonisamide	35 (3.8)
Lacosamide	24 (2.6)
HADS-D score (mean±SD)	8.3 ± 3.8
PHQ-2 score (mean±SD)	1.8 ± 1.7

control of seizures. The detail of seizure outcome of patients on monotherapy, duotherapy and polytherapy is presented in Table 2. Patients on monotherapy of any AED (older and newer) had the best seizure control as depicted by significantly higher percentage of seizure free patients compared to other groups (polytherapy including combination of both older and newer AEDs).

Effect on HADS-D score

Mild and clinically relevant depression occurred in 279 (29.9%) and 223 (23.9%) patients, respectively. The HADS-D score of patients on monotherapy, duotherapy and polytherapy was 6.7 ± 2.7, 8.01 ± 3.6, 10.4 ± 3.9, respectively. The difference in HADS-D score between monotherapy, duotherapy and polytherapy was statistically significant ($p < 0.001$) with score being highest for polytherapy and lowest for monotherapy. The HADS-D score was also studied individually in adolescents and adults separately in Table 3.

The HADS-D score varied significantly for monotherapies of various AEDs as shown in Fig. 1. Patients on LEV exhibited significantly higher HADS-D score in comparison to patients on PHT ($p < 0.001$), CBZ ($p < 0.001$) and VPA ($p < 0.05$).

Effect on PHQ-2 score

The PHQ-2 score of patients on monotherapy, duotherapy and polytherapy was 1.46 ± 1.6, 1.76 ± 1.7, 2.23 ± 1.7, respectively. A total of 216 (23.2%) patients exhibited clinically relevant PHQ-2 score. Patients on polytherapy exhibited significantly higher PHQ-2 score in comparison to those on one or two AEDs ($p < 0.001$). However, the PHQ-2 score did not differ significantly between patients on monotherapy and duotherapy ($p = 0.06$). Also, there was no significant difference in PHQ-2 score among patients on monotherapy of different AEDs (PHT, CBZ, VPA and LEV). The PHQ-2 score was also studied individually among adolescents and adults separately as presented in Table 3.

Factors responsible for occurrence of depression in patients with epilepsy

Multivariate regression analysis revealed that factors like age, gender, age at onset of seizures, type of seizures and duration of treatment did not have any correlation with occurrence of depression in PWE. However, frequency of seizures, number of prescribed AEDs and AED load were associated with presence of depression in PWE ($p < 0.001$).

Effect of seizure frequency on HADS-D and PHQ-2 score

In patients having good control of seizures i.e. no seizure in last one year or one seizure in 6 months, HADS-D score was significantly lower than that of patients having seizure weekly or monthly ($p < 0.001$). Patients in category 4 having daily or weekly seizures had significantly higher HADS-D score than patients in other categories i.e. 1 ($p < 0.001$), 2 ($p < 0.001$) and 3 ($p < 0.01$) (Table 4).

PHQ-2 score did not differ significantly between patients having good control of seizures i.e. category 1 (no seizure from

Table 2
Detail of seizure outcome of patients on different drug regimens i.e. monotherapy, duotherapy and polytherapy of antiepileptic drugs. Data represented as n (%).

Treatment (n)	Seizure free (no seizure in a year)	At least one seizure in 6 months	At least one seizure in a month	At least one seizure in a week
Monotherapy (316)	195 (61.7)	68 (21.5)	49 (15.5)	4 (1.3)
Duotherapy (325)	164 (50.5)	64 (19.7)	80 (24.6)	17 (5.2)
Polytherapy (292)	97 (33.2)	47 (16.1)	99 (33.9)	49 (5.3)

Table 3
Hospital anxiety depression score (HADS-D) and Patient Health Questionnaire (PHQ-2) in adolescents and adults on different antiepileptic drug regimens i.e. Monotherapy, Duotherapy and Polytherapy.

Treatment	Adolescents		Adults	
	HADS-D	PHQ-2	HADS-D	PHQ-2
Monotherapy	6.38 ± 2.35	1.44 ± 1.43	6.82 ± 2.93	1.47 ± 1.61
Duotherapy	$7.81 \pm 3.48^{**a}$	1.61 ± 1.66	$8.12 \pm 3.67^{**a}$	1.84 ± 1.68
Polytherapy	$10.27 \pm 3.63^{***ab}$	$2.35 \pm 1.69^{**ab}$	$10.49 \pm 4.07^{***ab}$	$2.15 \pm 1.65^{***a}$

Data represented as mean ± SD. $^{**}p < 0.01$; $^{***}p < 0.001$; a- as compared to monotherapy; b- as compared to duotherapy.

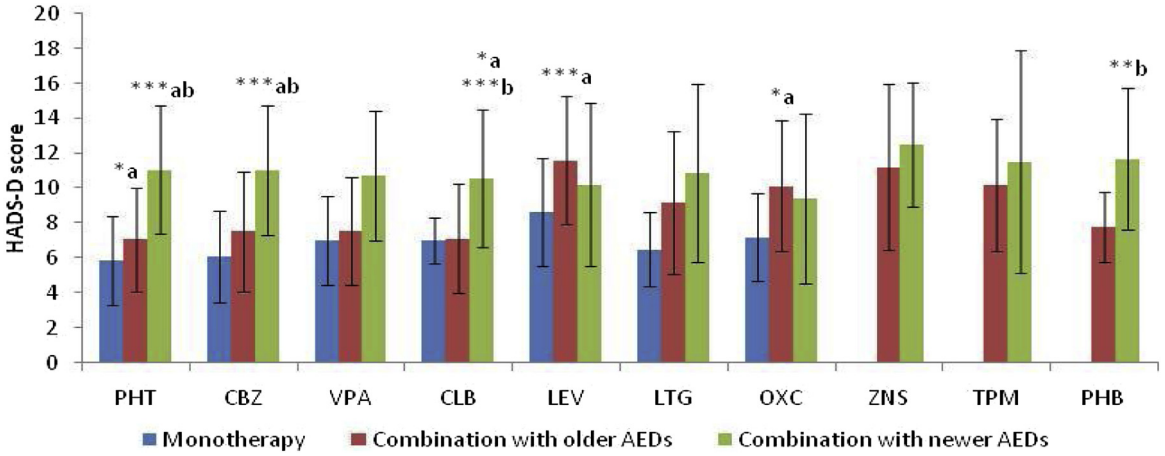

Fig. 1. Hospital anxiety depression (HADS-D) score in patients on different antiepileptic drugs (AEDs); (1) monotherapy; (2) combination of older AEDs only; (3) combination with newer AEDs; *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$; a- as compared to monotherpay; b- as compared to combination of older AEDs.

Table 4
Hospital anxiety depression score (HADS-D) and Patient Health Questionnaire (PHQ-2) in patients with good (category 1 and 2) and poor (category 3 and 4) seizure control on different antiepileptic drug regimens. (1) Monotherapy of older AEDs; (2) monotherapy of newer AEDs; (3) combination of older with older AEDs; (4) combination of older with newer AEDs; (5) combination of newer with newer AEDs. *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$; a- as compared to monotherapy of older AEDs; b- as compared to monotherapy of newer AEDs; c- combination of older with older AEDs.

S.No.	Groups	HADS-D score		PHQ-2 score	
		Good seizure control	Poor seizure control	Good seizure control	Poor seizure control
1	Monotherapy of older AEDs	6.3 ± 2.6	6.61 ± 2.4	1.36 ± 1.6	1.35 ± 1.3
2	Monotherapy of newer AEDs	7.98 ± 2.9*a	9.57 ± 3.1	1.91 ± 1.5	2.29 ± 1.8
3	Combination of older with older AEDs	6.68 ± 2.9	8.39 ± 3.2	1.23 ± 1.4	1.95 ± 1.8
4	Combination of older with newer AEDs	10.46 ± 3.9*abc	10.67 ± 3.9***ac	2.28 ± 1.7	2.46 ± 1.7
5	Combination of newer with newer AEDs	9.83 ± 6.2	9.67 ± 3.5	1.67 ± 1.5	2.67 ± 1.7

last one year) and category 2 (one seizure in 6 months). The PHQ-2 score of patients in category 1 was significantly lower than that of patients with poor control of seizures i.e. category 3 ($p < 0.01$) and category 4 ($p < 0.001$). Patients suffering from daily seizures were found to have significantly higher PHQ-2 score in comparison to patients having weekly ($p < 0.05$) or monthly seizures ($p < 0.05$).

Effect of AED load on HADS-D and PHQ-2 score

Mean AED load of each patient on different treatment regimens was also calculated. The AED load of patients on monotherapy (0.73 ± 0.35) was significantly less than that of duotherapy (0.83 ± 0.34) ($p < 0.01$) and polytherapy (0.93±0.29) ($p < 0.001$). The mean AED load of duotherapy was significantly lower than that with polytherapy ($p < 0.001$). After analysis of AED load of individual drugs in different treatment regimens, polytherapy was found to elicit significantly higher AED load in comparison to both monotherapy and duotherapy except for phenytoin and clonazepam where no significant change in AED load was found between treatment regimens.

Multivariate regression analysis revealed the direct relationship of mean AED load with HADS-D and PHQ-2 score. HADS-D score varied significantly with AED load in patients on LEV ($p < 0.001$), VPA ($p < 0.001$), CLB ($p < 0.01$), ZNS ($p < 0.01$), TPM ($p < 0.05$) and OXC ($p < 0.01$). However, there was no significant correlation between AED load and HADS-score of patients on PHT, CBZ, PHB and LTG.

In addition, AED load of LEV ($p < 0.001$) and OXC ($p < 0.05$) significantly affected the PHQ-2 scores. For other AEDs, the correlation of PHQ-2 score with AED load was not significant.

Effect of older and newer antiepileptic drugs on HADS-D and PHQ-2 score

Mean HADS-D score for combination of newer AEDs (12 ± 4.2) was significantly higher than that of combination of older AEDs (7.21 ± 3.1; $p < 0.001$), monotherapy of older AEDs (6.35 ± 2.6; $p < 0.001$) and newer AEDs (8.68 ± 2.9; $p < 0.05$). Although combination of older and newer AEDs also elicited lower HADS-D score (10.65 ± 3.8) than combination of only newer AEDs, the difference was not statistically significant. Therefore, newer AEDs either in monotherapy or in combination resulted in higher HADS-D score.

For the purpose of analysis, data was combined for polytherapy of newer AEDs, irrespective of other drugs in the combination. Among newer AEDs, patients on LEV ($p < 0.001$) and OXC ($p < 0.05$) had significantly higher HADS-D score as compared to their monotherapy. However, no significant difference was found in HADS-D score of patients having monotherapy and polytherapy of VPA, LTG, ZNS and TPM (Fig. 1).

Mean PHQ-2 score for combination of newer AEDs (3.4 ± 1.4; $p < 0.01$) as well as combination of newer and older AEDs (2.35 ± 1.6; $p < 0.001$) was significantly higher than that of combination of older AEDs (1.49 ± 1.6). Although, mean PHQ-2 score of patients on monotherapy of newer AEDs (2.05 ± 1.6) was higher than those on monotherapy of older AEDs (1.36 ± 1.5), it was not statistically significant. Hence, mean PHQ-2 score was significantly higher with newer AEDs when given in polytherapy as compared to monotherapy (older and newer AEDs separately) as well as polytherapy of older AEDs ($p < 0.001$).

Patients on combination of older and newer AEDs had significantly higher PHQ-2 score as compared to patients on

monotherapy (PHT, CBZ and CLB) and combination of older AEDs ($p < 0.001$). The difference in PHQ-2 score of all other older and newer AEDs did not differ significantly among the groups (Fig. 2).

Discussion

Being a long-standing taboo, depression in epilepsy remains underdiagnosed and undertreated [22]. It has been assumed that epilepsy and depression exhibit bidirectional relationship due to a normal emotional response to a chronic disease like epilepsy. Epilepsy represents a model for brain–behavior associations as seizures have an effect on behavior, and behavior affects seizures. Patients with refractory epilepsy, having an insult to limbic area, may lead to more behavior changes than patients with controlled seizures [23]. In the present study, HADS-D score were significantly higher in patients on polytherapy as compared to those on monotherapy which is in contradiction to the results of a study by Gomez-arias et al. where HADS-D score did not vary with the number of AEDs prescribed [20].

In the present study, significant association was not observed between broad seizure type and development of depression. In our study, almost half the patients had generalized and the other half had focal seizures. The classification was not elaborated into further subdivisions. Grabowska-Grzyb et al. reported that depressed patients with focal seizures were more likely to have complex partial seizures. They did not include patients with generalized seizures [24]. Owolabi et al. [25] subdivided generalized and focal seizures but more than 80% of their participants had generalized seizures and they did not find correlation of seizure type with depression. Whether different types of generalized or focal seizures would have a bearing on the occurrence of depression or not, remains to be studied.

Patients having poor seizure control showed significantly higher HADS-D and PHQ-2 score, suggesting that depressive symptoms in PWE may correlate with seizure control, which in turn implies that the disease process itself may be associated with depression. This is contradictory to the above mentioned study where HADS-D score did not vary with seizure frequency [20]. Moreover, seizure-free patients have been demonstrated with better scores than those with continual seizures and scores were not interrelated to the type or number of AEDs used [6].

The incidence of depression varied with seizure frequency which may predict variation in depression score over time. A bidirectional relationship between depression scores and seizure frequency in PWE was shown by Thapar et al. [26]. The effect of recent seizures on long-term depression scores could be through a direct neurobiological change [27] and in turn depression may be a risk factor for the onset of epilepsy [7,28]. However, the link between seizures and depression could also arise through other mechanisms such as disruption of routine life and negative emotions, which could manifest as behavior changes, altered medication adherence and other risky behaviors such as suicidal tendencies, increased alcohol intake etc.

According to current understanding, patients having poor control of seizures and taking more than one AED, may have higher incidence of depression [29]. In the present study, the HADS-D and PHQ-2 scores were significantly higher in patients on polytherapy of older with newer AEDs as well as only newer AEDs in comparison polytherapy of only older AEDs. This indicates higher incidence of depression with use of newer AEDs. There is some evidence linking depression with the use of newer AEDs [4], but there is no study comparing depression in PWE on older versus newer AEDs in Indian population. Among newer AEDs, patients on LEV and OXC (in combination with older AEDs) had significantly higher HADS-D score as compared to their monotherapy.

The present study demonstrated a positive correlation between number of AEDs and AED load with presence of depression in PWE. However, Canevini et al. [18] suggested that AEDs' toxicity is more closely related to the total "load" of the drug (the sum of all ratios of actually prescribed daily doses and the mean therapeutic dose of each drug) than to the number of administered AEDs. It was found that duration of epilepsy had significant effect on occurrence of depression in PWE of Northwestern Nigeria [25]. The results of our study did not show any significant association between duration of treatment and depression.

Levetiracetam, was the most commonly prescribed newer AED in the present study and was found to be associated with significantly higher HADS-D score in comparison to other older AEDs (PHT, CBZ, VPA). It has been reported to be associated with depression and suicidal tendency previously [30]. A recent study by Wieshman et al. also suggested the association of LEV with depression and other mood disorders [31]. The other AEDs, including TPM and ZNS, also have been reported to exert negative effects on mood and cognition. In our study, patients on LEV and OXC (in combination with older AEDs) had significantly higher HADS-D score as compared to their monotherapy. An earlier study has demonstrated higher risk of depression with the use of LEV and OXC [32].

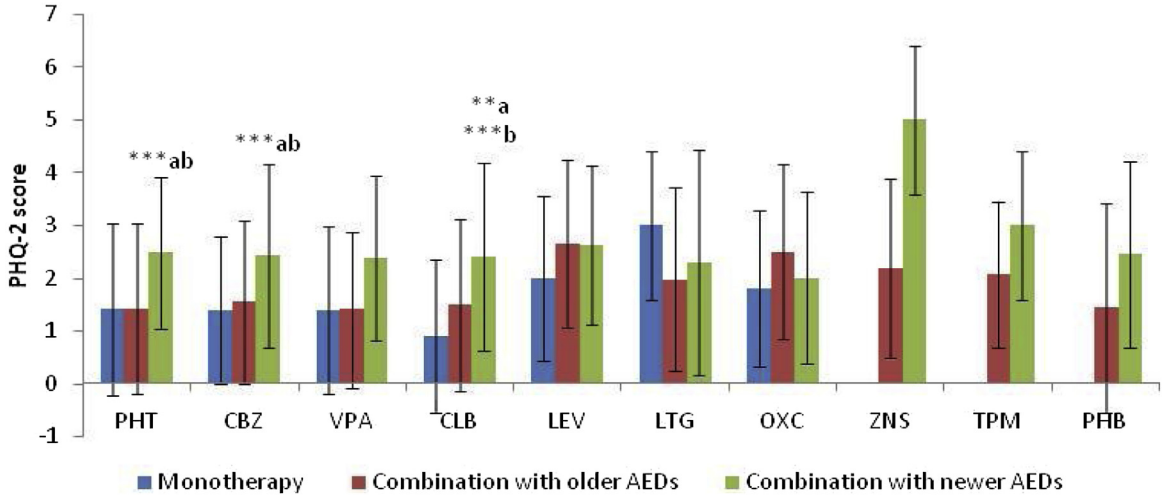

Fig. 2. Patient Health Questionnaire (PHQ-2) score in patients on different antiepileptic drugs in the study cohort. (1) Monotherapy; (2) combination of older AEDs only; (3) combination of newer AEDs; $^{**}p < 0.01$, $^{***}p < 0.001$; a- as compared to monotherpay; b- as compared to combination of older AEDs.

It has been hypothesized that frequent seizures distort the balance of GABA-ergic and glutamatergic activity which in turn produces neuropsychiatric disturbances like depression. VPA and LTG have been regarded as drugs with anti-suicidal properties as they improve cognitive function and mood. Potentiation of GABAergic neurotransmission seems to be more frequently associated with mood deterioration. The sturdy link between depression and epilepsy might also be due to variable medication adherence. The fear of recurrent seizures in PWE may also contribute to greater incidence of depression [33].

The incidence of clinically significant depressive symptoms was observed to be present in approximately one fourth of our study population. Many a times health care providers hub entirely on medical aspects of the disease and neglect the indirect disease burden including neurobehavioral adverse effects like depression etc. Not just depression but neurocognitive functioning also influence quality of life in patients with epilepsy [34]. These PWE may also bump into disgrace due to unpredictable and uncontrollable seizures leading to fear and concern for others. Therefore, the treating physicians should also emphasize on the utmost care of these patients and modify their medication as per neurobehavioral symptoms.

The present study used preliminary tests i.e. HADS-D and PHQ-2 scales for the screening of depressive symptoms rather than diagnostic tools. Both the tests have been appropriately used in the current study as screening instruments rather than diagnostic tools. Moreover, these tests are the most prominent and rapid tests to diagnose depressive symptoms in PWE in a tertiary care centre. These tests provide us the quick preliminary information to further evaluate those patients for the diagnosis of depression. They also provide the immediate information to the treating physician for monitoring the pharmacotherapy of the PWE. A HADS-D score of >14 for example do not necessarily mean that the respondent has clinical depression. Further assessment would be required before that conclusion is reached. Association is not the causality. The patients might be having higher evidence of depression or the vice- versa.

It demonstrated the association between depression and use of AEDs, their load and occurrence of seizures. Depression is more commonly associated with combination of newer AEDs in comparison to older AEDs. The findings suggest that there should be close monitoring of patients on newer AEDs especially LEV, for depression which can occur even in the absence of other risk factors or mood disturbances. Depression should be routinely evaluated during clinical trials to allow comparison of psychiatric safety of AEDs.

Limitations of the study

Although, this study has preliminary evaluated the occurrence of depressive symptoms in PWE and their correlation with disease activity (seizure score), number of AEDs (monotherapy and polytherapy) and AED load (PDD/DDD) in Indian population, it has certain limitations. Firstly the study population, being recruited from tertiary care referral study centre, may not be the true representation of PWE in general population. There were more patients having poor seizure control and on multiple AEDs. Secondly, patients taking only newer AEDs (either monotherapy or combination of newer AEDs) were few, precluding meaningful conclusion from these groups. Mood assessment was done in a cross sectional manner in patients who were already taking AEDs lacks association between their counterparts in development of depression. Thirdly, use of very basic tools to evaluate depression sometimes also lead to misinterpretation of the data. Lastly, the analysis is complicated by the use of varied treatment regimens and doses in routine clinical practice.

Conclusion

Newer AEDs are more commonly associated with depression as compared to older AEDs. Depression was found to be associated with frequency of seizures, number of antiepileptic drugs and drug load in PWE. Routine counseling of PWE may benefit them and improve their quality of life. Prospective controlled studies on treatment naive patients are required to firmly establish the association between newer AEDs and depression.

Conflict of interest

None of the authors has any conflict of interest to disclose.

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