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A COMPARATIVE STUDY ON EFFICACY OF LEVETIRACETAM WITH OTHER ANTIEPILEPTIC DRUGS BY ASSESSING BEHAVIOURAL AND COGNITIVE CHANGES USING DSM-V AND MMSE SCALES

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ABSTRACT

Background: Epilepsy is the second common, frequently encountered neurological condition that imposes heavy burden on individual, families, and on healthcare systems. In addition to seizure-control, many of the treatment failures are due to cognition-behavioural changes which were reported as an adverse effect. **Aim:** To compare the efficacy of Levetiracetam with other antiepileptic drugs by assessing behavioural and cognitive changes using various scales. **Method:** This is a Prospective Case-Control study conducted in Guntur City Hospitals. A total of 400 sample were included, out of which 200 epileptic patients who were on antiepileptic's and 200 are Healthy-controls. Both cognitive & behavioural changes were compared among Healthy-controls and Epileptic patients using Mini-mental scale examination and Diagnostic statistical manual of mental disorders scales, and also compared safety and efficacy of Levetiracetam with other antiepileptics. **Results:** In our study, knowledge about Medications and Life style modifications was provided using Counselling Aids. Among 200 Epileptic patients, 100 subjects were on Levetiracetam. Out of which cognitive changes (14%), behavioural changes(24%), both cognitive-behavioural changes(8%), whereas no changes in 54% patients. Remaining 100 Subjects were on other

AED'S. Among them cognitive changes (9%), behavioural changes (14%) and both changes (3%) were observed; no changes observed in 74% patients. **Conclusion:** The Patients with epilepsy become seizure-free with the first prescribed AED in daily-clinical practice. In addition to seizure-control, the overall effectiveness is also determined by adverse-events, which are responsible for approximately 1/3rd of treatment failures. The study concludes that Cognitive-behavioural sideeffects occur more frequently in patients prescribed with Levetiracetam than other antiepileptics.

KEYWORDS: Epilepsy, Cognition, Behaviour, Levetiracetam.

INTRODUCTION

The word "epilepsy" has its origin in ancient Greece which means "to seize, possess, orafflict".[1] Epilepsy is a neurological disorder characterized by chronic predisposition marked by sudden recurrent episodes of sensory disturbance, loss of consciousness, or convulsions, associated with abnormal electrical activity in the brain, which requires typically two unprovoked seizures.[2,3] A seizure is defined as an abnormal, disorderly discharging of the brain's nerve cells, resulting in a temporary disturbance of motor, sensory, or mental function.[4]

Epilepsy is the commonest neurological condition affecting people of all ages, race and social class.[5] The incidence of a first unprovoked seizure was 61 per 100,000 compared to the incidence of epilepsy of 44 per 100,000.[6] The International League against Epilepsy (ILAE) has proposed two major schemes for the classification of Seizures and Epilepsies. they are The International Classification of Epileptic Seizures and the International Classification of the Epilepsies and Epilepsy Syndromes.[7,8] · Seizure activity is characterized by paroxysmal discharges occurring synchronously in a large population of cortical neurons. This is characterized on EEG as a sharp wave or spike.[9]

The epileptic seizures may be associated with cognitive and behavioural alterations in infants and adults.[10] Psychiatric and behavioural side effects (PBSEs) are highly prevalent in patients taking antiepileptic drugs (AEDs).[11] Levetiracetam (LEV) is one of the newest AEDs, marketed worldwide. Levetiracetam is most commonly used as a monotherapy to treat Epilepsy in clinical practice. In addition to seizure control, many of the treatment failures were due to cognition and behavioural changes which are highly prevalent in patients taking antiepileptic drugs (AEDs) especially Levetiracetam. The cognitive and Behavioural Side

effects of Antiepileptic Drugs can be examined by using Mini-Mental State Examination (MMSE) and Diagnostic statistical manual of mental disorders cross cutting level 1 and 2 scales respectively.[12] This study is mainly intended to assess the extent of behavioural and cognitive changes that occurs with the continuous use of antiepileptic drugs majorly Levetiracetam with other antiepileptic drugs (Phenytoin, Carbamazepine, Sodium valproate, Clobazam, Lamotrigine).

OBJECTIVES

1. To determine the patient therapeutic outcomes i.e. both Cognitive and Behavioural changes of antiepileptic drugs.
2. To improve patient health related quality of life by providing patient information leaflets.
3. To provide patients (as appropriate) and families with consistent information as well as necessary patient education.

MATERIALS AND METHODS

The current study was a Prospective Case-Control study conducted in Guntur City Hospitals, located in Guntur, Andhra Pradesh, India. The data collection for the study was conducted between September 2018 to February 2019.

The study had included all men and women aged above 17yrs and up to 60yrs. Both In-Patient and Out Patients were also included.

Specific populations like Neonates, infants, children, pregnant women and comatose patients were excluded from the study. Patients who are having other Neurological and Psychiatric disorders and Patients who are under combinational antiepileptic therapy were excluded from the study.

Data on demographic parameters and clinical profile was documented in a structured proforma. The difference in Cognition and Behavioural changes among healthy volunteers and diseased groups were assessed by using standard Questionnaire MMSE and DSM-V criteria. The study was approved by institutional human ethics committee and informed written consent was obtained from all the participants.

Data was analyzed using mean and standard deviation for quantitative variables and frequency and proportion for categorical variables using Chi- Square and P-Test.

RESULTS

A Comparative Study on Efficacy of Levetiracetam with Other Antiepileptic Drugs by Assessing Behavioural and Cognitive Changes using DSM V and MMSE scales. The study was conducted during the period of September 2018 to February 2019.

Table 01: Distribution of Study Population.

Type of population	Sample size	Percentage
Healthy Volunteers	200	50%
Patients using Levetiracetam	100	25%
Patients using other Antiepileptic's	100	25%
Total	400	100%

The 400 study population is categorized in to 3 groups i.e. 50% were Healthy volunteers (n=200), 50% were epileptic Patients (n=200) among which 25% Subjects were using Levetiracetam (n=100) and 25% Subjects were using other AED'S (n= 100).(Tab.1,Fig.1)

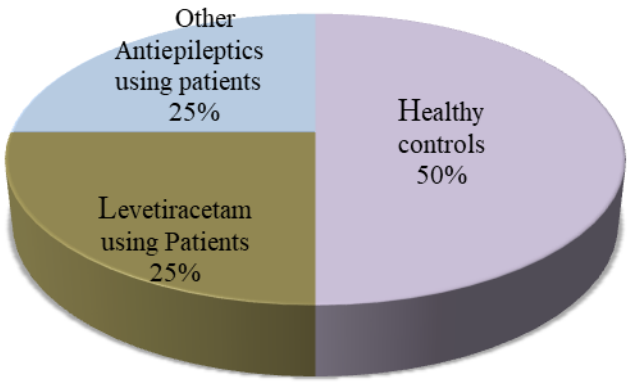

Figure 01: Distribution of Study Population.

Table 02: Age Wise Distribution of Healthy Volunteers and Diseased Population.

Age Group	Healthy Group	Percentage	Diseased Population	Percentage
18- 27	21	10.5%	99	49.5%
28-37	48	24.0%	32	16.0%
38-47	45	22.5%	39	19.5%
48-57	47	23.5%	16	8.0%
58- 60	39	19.5%	14	7.0%
Total	200	100%	200	100%
			Mean ± SD = 32.95 ± 12.24.	

Among 200 Healthy volunteers, Majority of population fall between age group of 28-37years i.e. 48 (24%) followed by 48-57 years 47 (23.5%) and the least was found in18-27 years 21 (10.5%)(Tab.2, Fig.2). Among 200 Diseased population, Majority of population fall between age group of 18-27years i.e. 99 (49.5%) followed by 38- 47years 39 (19.5%) and the least

was found in58-60 years 14(7.0%). The mean age of diseased population was 32.95 ± 12.24.(Tab.2,Fig.3)

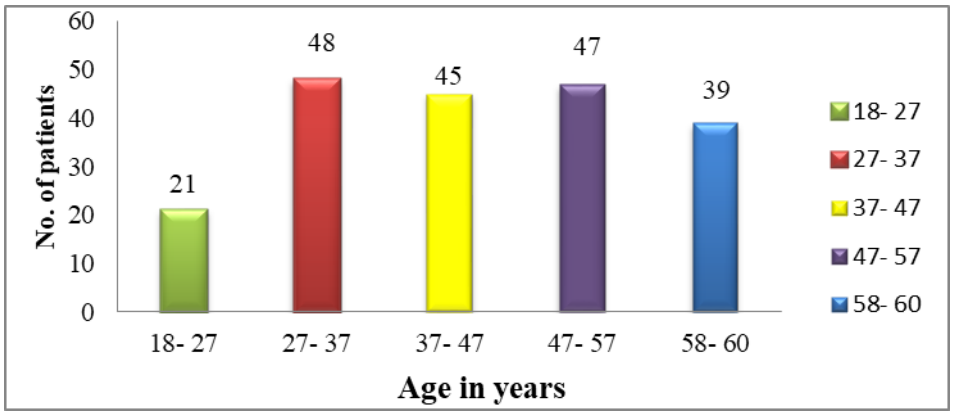

Figure 02: Age Wise Distribution of Healthy Volunteers.

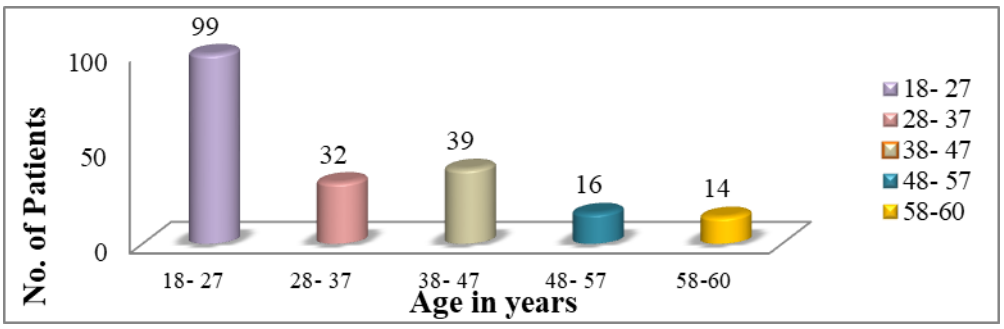

Figure 03: Age Wise Distribution of Diseased Population.

Table 03: Gender Wise Distribution of Study Population.

Gender	Healthy Group	Percentage	Diseased population	Percentage
Males	102	51.0%	133	66.5%
Females	98	49.0%	67	33.5%
Total	200	100%	200	100%

Total number of population included in the study was 400 members. Out of 400 populations, majority of participants were identified as males in both Healthy and diseased population group.(Tab.3,Fig.4).

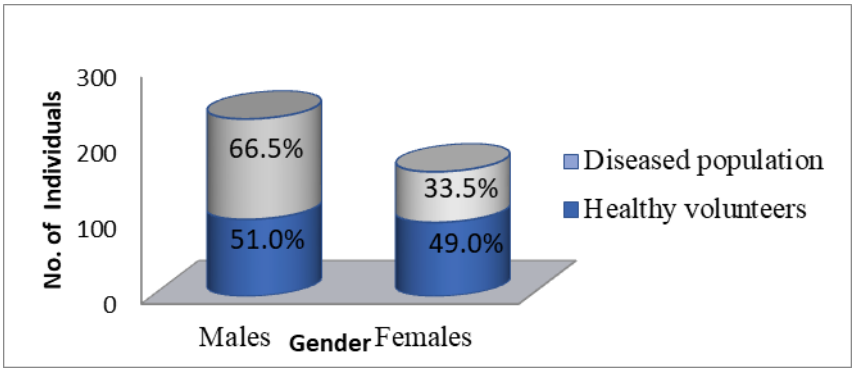

Figure 04: Gender Wise Distribution of Study Population.

Table 04: Risk Factor Based Distribution of Epileptic Patients.

Risk factor	Total	Percentage
Age	19	9.5%
Genetics	67	33.5%
Idiopathic	114	57.0%
Total	200	100%

Among 200 epileptic patients majority of the population was diagnosed with epilepsy due to the Unknown cause i.e. Idiopathic 57.0% (n= 114), Genetics 33.5% (n= 67) and Age 9.5% (n=19).(tab.4,Fig.5)

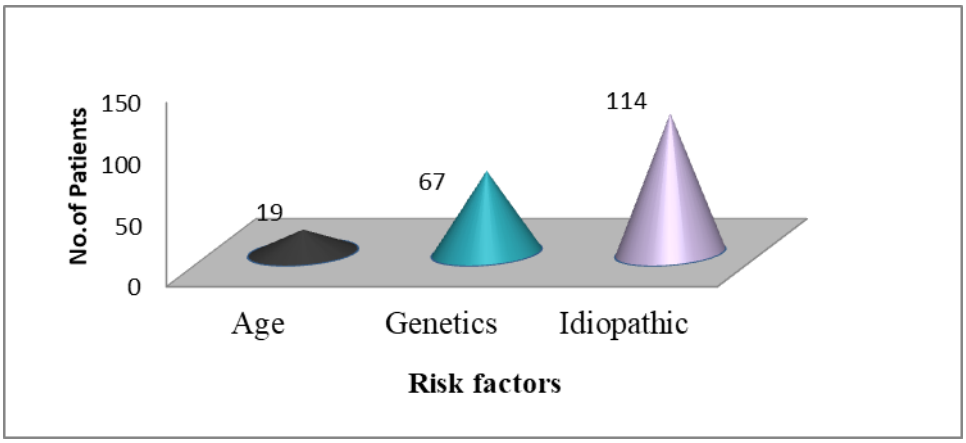

Figure 05: Risk Factor Based Distribution of Epileptic Patients.

Table 05: Seizure Type Based Distribution.

Type	Total	Percentage
Myoclonic seizures	4	2.0%
Late onset seizures	10	5.0%
Generalised tonic - clonic seizure (GTCS)	114	57.0%
Childhood seizures	26	13.0%
Granuloma seizures	5	2.5%
Complex partial seizures	18	9.0%

Simple partial seizures	13	6.5%
Status epilepticus	3	1.5%
Refractory epilepsy	3	1.5%
Nocturnal seizures	1	0.5%
Gliotic seizures	3	1.5%
Total	200	100%

Among the 200 members, Patients with Myoclonic seizures 2.0% (n= 4), Late onset seizures 5.0% (n= 10), Generalised tonic - clonic seizure (GTCS) 57.0% (n= 114), Childhood seizures 13.0% (n=26), Granuloma seizures 2.5% (n= 5), Complex partial seizures 9.0% (n= 18), Simple partial seizures 6.5% (n= 13), Status epilepticus 1.5% (n= 3), Refractory epilepsy 1.5% (n= 3), Nocturnal seizures 0.5% (n=1), Gliotic seizures 1.5%(n=3).(Tab.5,Fig.6)

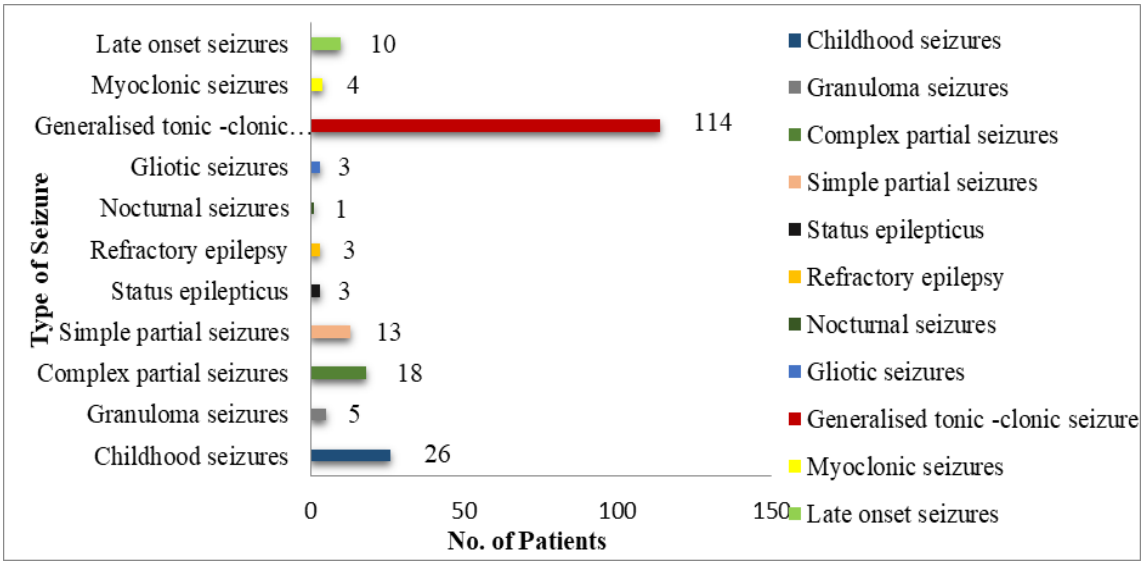

Figure 06: Seizure Type Based Distribution.

Table 06: Patients on AED Therapy.

Antiepileptic drugs	No. of patients	Percentage
Levetiracetam	100	50.0%
Sodium Valproate	31	15.0%
Phenytoin	26	13.0%
Carbamazepine	26	13.0%
Clobazam	13	7.0%
Lamotrigine	4	2.0%
Total	200	100%

We had Collected the data based on the AED used by the individual patient i.e., Levetiracetam 50% (n= 100), Sodium Valproate 15.0% (n= 31), Phenytoin 13.0% (n= 26), Carbamazepine 13.0% (n= 26), Clobazam 7.0% (n= 13), Lamotrigine 2.0% (n =4).(tab.6,Fig.7)

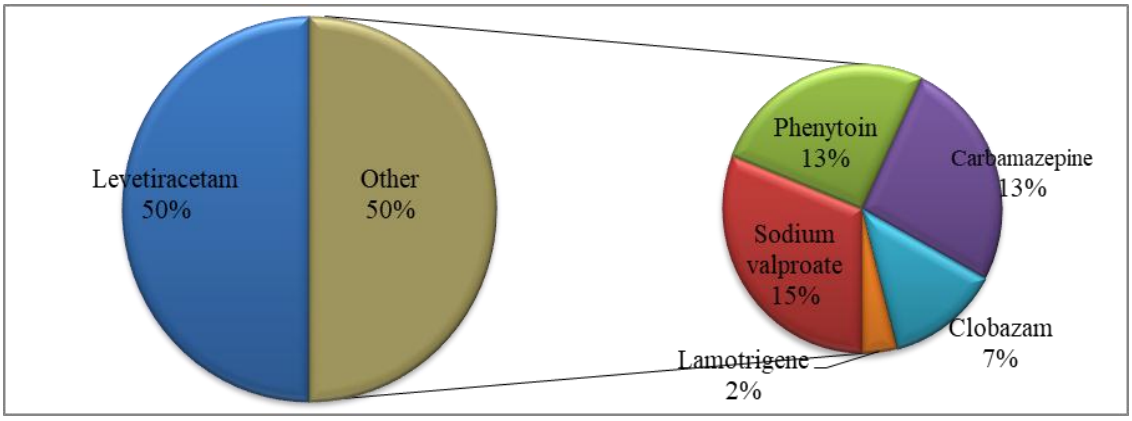

Figure 07: Patients on AED Therapy.

Table 07: Comparision of Cognitive and Behavioural changes of both Healthy Volunteers and Diseased Population.

Parameters assessed	Healthy volunteers	Percentage	Diseased population	Percentage	X^2value	P value
Cognitive changes	4	2.0%	23	11.5%	51.42	<0.0001
Behaviouralchanges	10	5.0%	38	19.0%		
Both	0	0%	11	5.5%		
No change	186	93.0%	128	64%		
Total	200	100%	200	100%		

In healthy volunteers (n= 200) the cognitive changes of 2.0% (n= 4), Behavioural changes of 5.0% (n= 10) were observed and 93.0% (n=186) were having no change. In Epileptic patients (n= 200) the cognitive changes of 11.5% (n= 23), Behavioural changes of 19.0% (n= 38), Both C&B changes 5.5% (n= 11) were observed and 64.0% (n=128) were having no change.(tab.7,Fig.8)

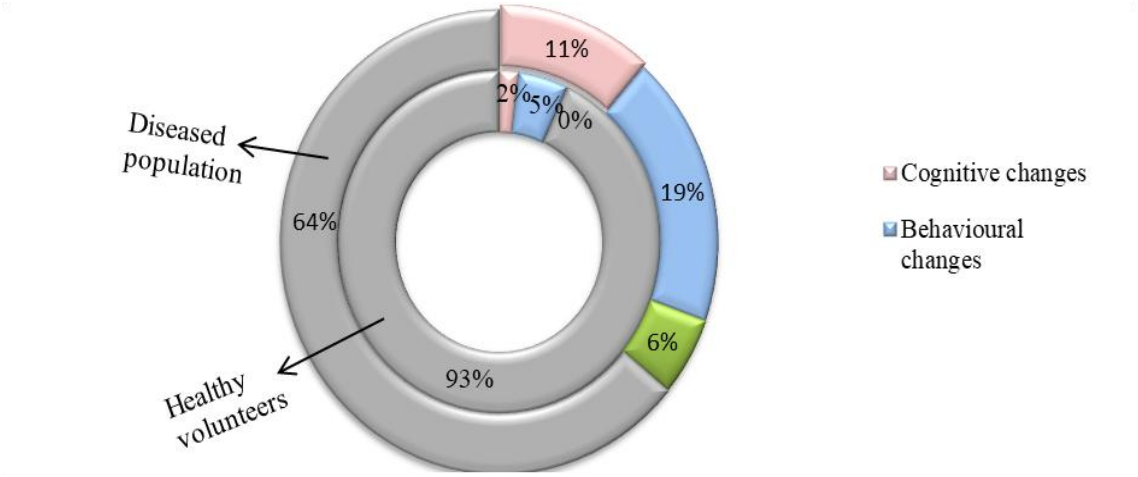

Figure 08: Comparison of Cognitive and Behavioural changes of both Healthy Volunteers and Diseased Population.

Table 08: Level of Severity of Cognition in Healthy Volunteers.

Level of severity	Healthy volunteers	Percentage
Mild	4	100%
Severe	0	0.0%

Among the Healthy volunteers having the cognitive change (n= 4), Mild were 100% (n= 4) and severe were 0.0%.

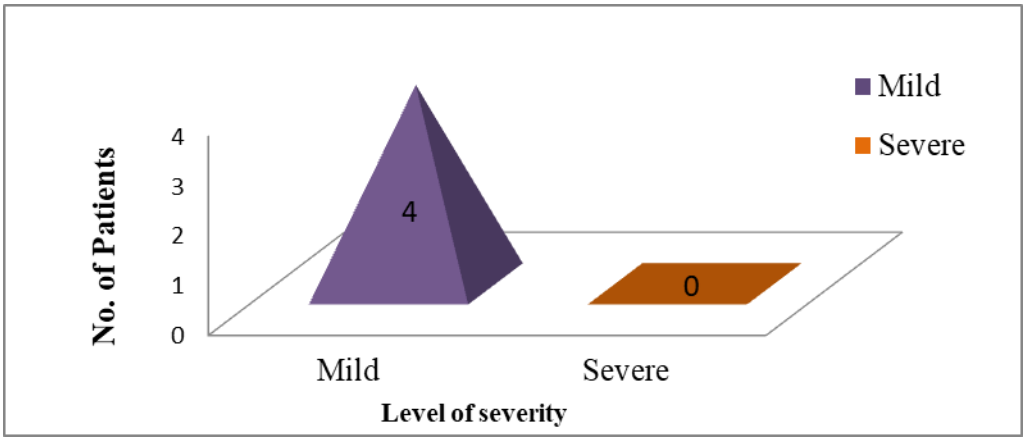

Figure 09: Level of Severity of Cognition in Healthy Volunteers.

Table 09: Level of Severity of Behavioural change in Healthy Volunteers.

Behavioural change	Mild	Moderate	Severe
Anger	4	0	0
Anxiety	1	0	0
Depression	3	0	0
Memory disturbances	0	0	0
Repetitive thoughts	0	0	0
Sleep disturbances	1	0	0
Unexplained aches	1	0	0

Among the volunteers mild Behavioural changes (n= 10) were observed i.e., Anger (n= 4), Anxiety (n= 1), Depression (n= 3), Sleep disturbances (n= 1), Unexplained aches (n= 1).(Tab.09,Fig.10)

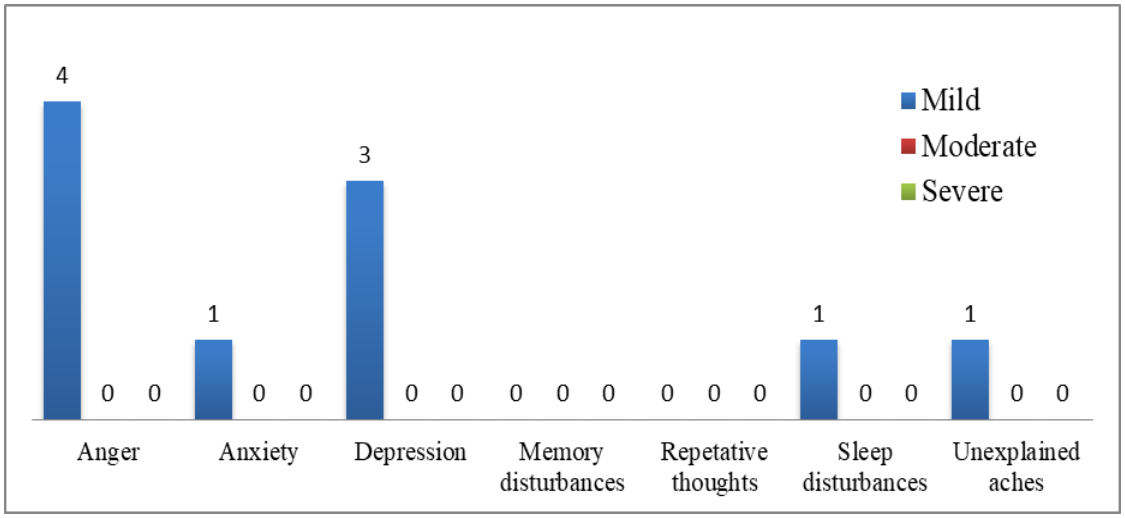

Figure 10: Level of Severity of Behavioural change in Healthy Volunteers.

Table 10: Comparision of Cognitive and Behavioural changes of both patients using Levetiracetam and other Antiepileptics.

Parameters assessed	Patients using Levetiracetam	Percentage	Patients using other AED's	Percentage	X^2Value	P value
Cognitive changes	14	14.0%	9	9.0%	20.3	< 0.0001
Behavioural changes	24	24.0%	14	14.0%		
Both	8	8.0%	3	3.0%		
No change	54	54.0%	74	74.0%		
Total	100	100%	100	100%		

In Patients using Levetiracetam (n= 100) the cognitive changes of 14.0% (n=14), Behavioural changes of 24.0% (n= 24), Both C&B changes of 8.0% (n= 8) were observed and 54.0% (n=54) were having no change. In Patients using other Antiepileptic's (n= 100) the cognitive changes of 9.0% (n= 9), Behavioural changes of 14.0% (n= 14), Both C&B changes 3.0% (n= 3) were observed and 74.0% (n=74) were having no change.(Tab.10,Fig.11)

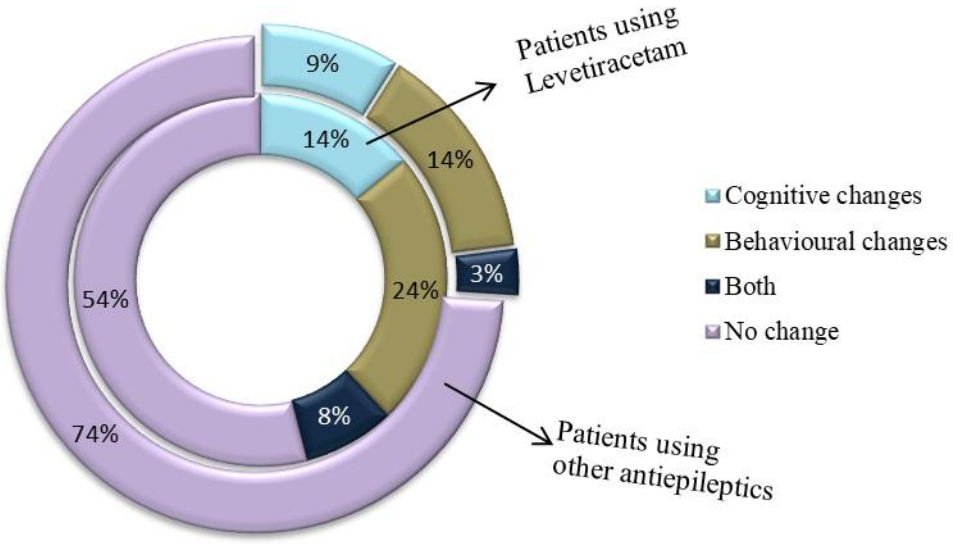

Figure 11: Comparision of Cognitive and Behavioural changes of both patients using Levetiracetam and other Antiepileptics.

Table 11: Level of Severity of Cognition in patients using Levetiracetam and other Antiepileptic's.

Level of severity	Patients using Levetiracetam	Percentage	Patients using other Antiepileptic's	Percentage
Mild	5	35.7%	7	77.7%
Severe	9	64.2%	2	22.2%
Total	14	100%	9	100%

Among the patients using Levetiracetam with cognitive impairment (n= 14), Mild were 35.7% (n= 5), severe were 64.2% (n= 9). In patients using other antiepileptic drugs with cognitive impairment (n= 9), Mild were 77.7% (n= 7), severe were 22.2% (n= 2). (Tab.11,Fig.12)

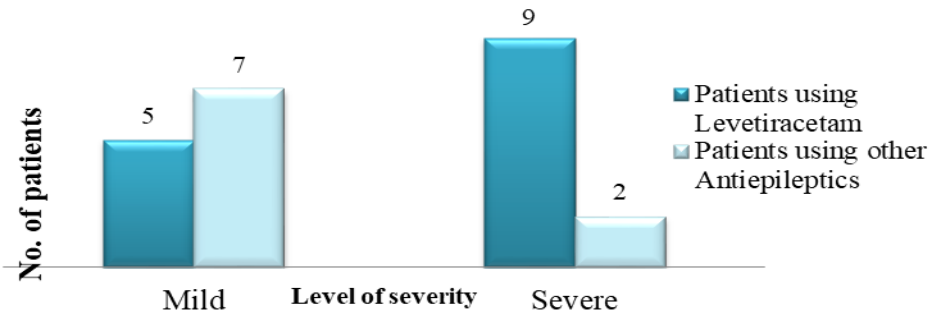

Figure 12: Level of Severity of Cognition in patients using Levetiracetam and other Antiepileptic's.

Table 12: Level of Severity of Behavioural change in Patients using Levetiracetam And Other Antiepileptic's.

Behavioural change	Patients using Levetiracetam	Percentage	Patients using other Antiepileptic's	Percentage
Anger	5	20.8%	3	21.4%
Anxiety	3	12.5%	1	7.14%
Depression	6	25.0%	3	21.4%
Memory disturbances	6	25.0%	3	21.4%
Repetitive thoughts	2	8.3%	0	0%
Sleep disturbances	1	4.2%	2	14.2%
Unexplained aches	1	4.2%	2	14.2%
Total	24	100%	14	100%

Among the patients using Levetiracetam with Behavioural change (n= 24), Anger 20.8% (n= 5), Anxiety 12.5% (n= 3), Depression 25.0% (n=6), Memory disturbances 25.0% (n=6), Repetitive thoughts 8.3% (n= 2), Sleep disturbances 4.2% (n= 1), Unexplained aches 4.2% (n= 1). Among the patients using other antiepileptic drugs with Behavioural change (n= 14), Anger 21.4% (n= 3), Anxiety 7.14% (n= 1), Depression 21.4% (n=3), Memory disturbances 21.4% (n=3), Sleep disturbances 14.2% (n= 2), Unexplained aches 14.2% (n= 2) (Tab.12,Fig.13,Fig 14).

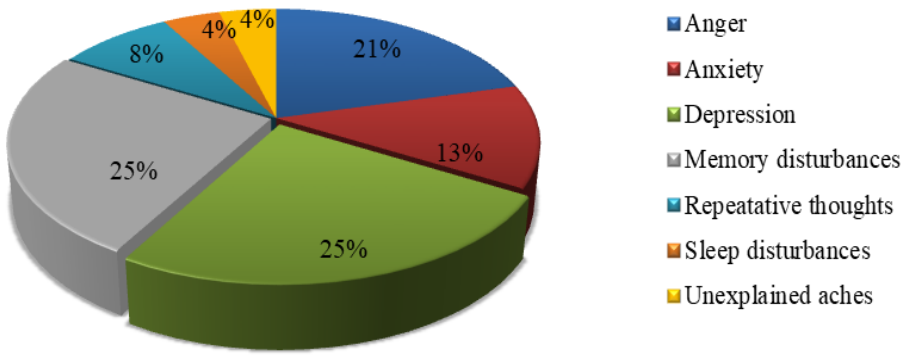

Figure 13: Level of Severity of Behavioural change in Patients using Levetiracetam.

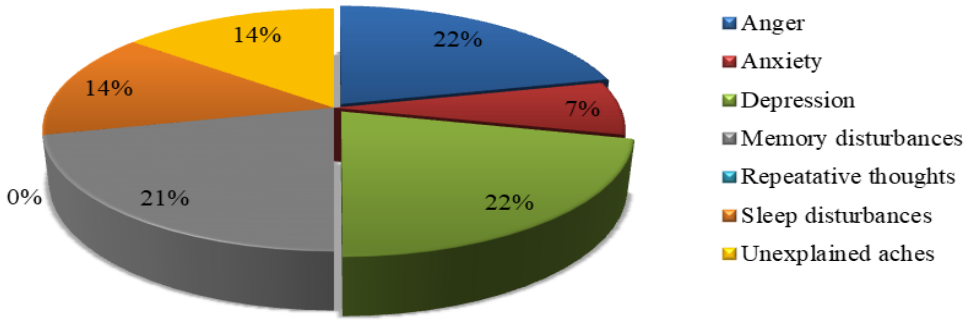

Figure 14: Level of Severity of Behavioural change in Patients using other Antiepileptic'

Table 13: Level of Severity of Both Cognitive and Behavioural change in Patients using Levetiracetam and other Antiepileptics.

Drugs used by Patients	Both Cognition and Behavioural changes	Percentage
Levetiracetam	8	72.7%
Other Antiepileptic's	3	27.3%
Total	11	100%

Cognitive and behavioural changes were mostly observed in patients using Levetiracetam than compared with other AED'S.(Tab.13,Fig.15).

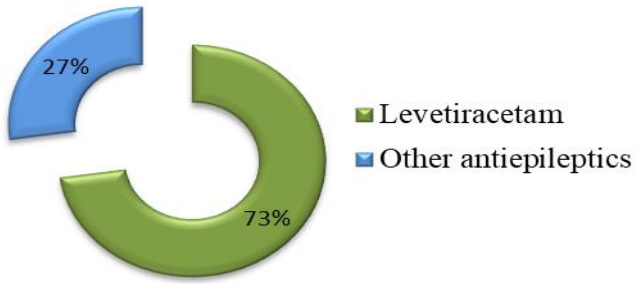

Figure 15: Level of Severity of Both Cognitive and Behavioural change in Patients using Levetiracetam and other Antiepileptics.

Table 14: Level of Severity of Behavioural change in Patients using Levetiracetam.

Behavioural changes	Mild	Moderate	Severe
Anger	0	2	3
Anxiety	1	2	0
Depression	1	1	4
Memory disturbances	0	1	5
Repetitive thoughts	0	1	1
Sleep disturbances	1	0	0
Unexplained aches	0	1	0

Among 100 Population, most of the patients having behavioural changes like Memory disturbances, Depression, Anger, Anxiety and least number of patients present with repetitive thoughts, sleep disturbances, unexplained Aches.(Tab.14,Fig.16)

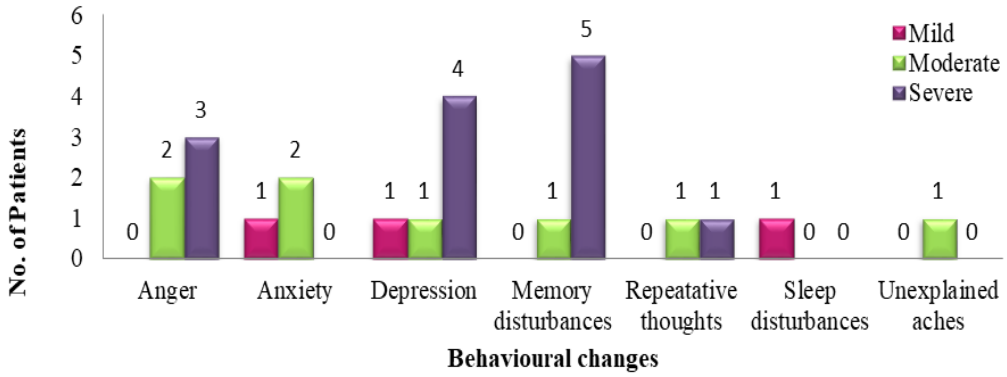

Figure 16: Level of Severity of Behavioural change in Patients using Levetiracetam.

Table 15: Level of Severity of Behavioural change in Patients using other Antiepileptic's.

Behavioural change	Mild	Moderate	Severe
Anger	2	1	0
Anxiety	1	0	0
Depression	2	1	0
Memory disturbances	2	0	1
Repetitive thoughts	0	0	0
Sleep disturbances	2	0	0
Unexplained aches	2	0	0

Out of 100 populations, most number of patients (who are on AEDS) having mild changes in their behaviour, least number of patients have moderate and severe changes.(Tab.15,Fig.17)

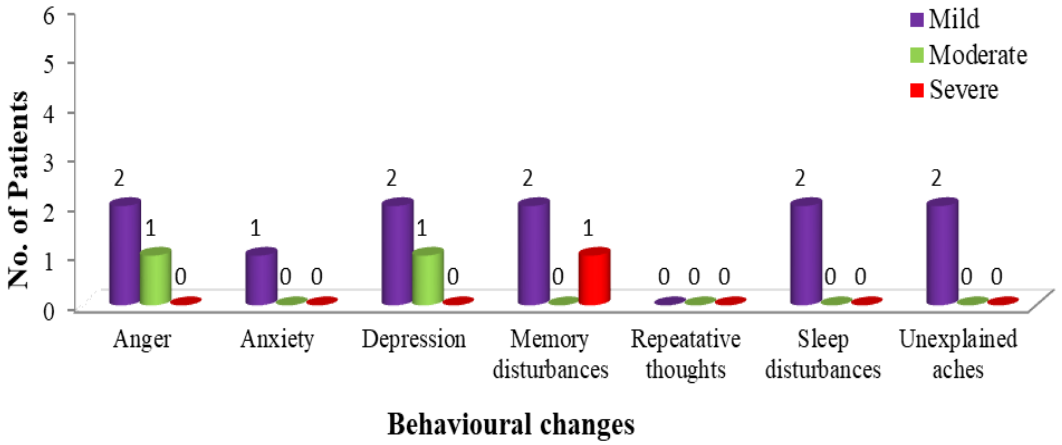

Figure 17: Level of Severity of Behavioural change in Patients using other Antiepileptic's.

DISCUSSION

In general practice, the therapeutic approach for Epilepsy condition is primarily empirical and the main aim of the physicians is to treat as specifically as possible. The present study was focused on Comparing the Efficacy of Levetiracetam with Other Antiepileptic Drugs by Assessing Behavioural and Cognitive changes using various scales (MMSE and DSM V).

Out of 400 population, Healthy volunteers (n=200) as a control group compared with the Diseased group (n=200) we assessed the impact of cognition and behavioural changes on individuals quality of life which was in accordance with the previous study.[13]

The study population includes 200 Healthy volunteers (n=200), and 200 epileptic Patients (n=200) among which 100 patients are using Levetiracetam (n=100), and 100 patients using other antiepileptic drugs (n=100). The control group of 200 randomly selected healthy individuals, matched with patients for age and gender in the study area. The control group had a significantly greater percentage of males. A data of 200 epileptic patients matching the inclusion criteria in Neurology department of corresponding study sited hospital was collected. Epilepsy is most common among all ages, especially in young people due to certain birth defects, Infections, trauma, structural abnormalities and stress during studies and at work. In this study, a total of 49.5% (n= 99) patients were in the age group of 18- 27 years.[14]

From our study we have observed that the prevalence of epilepsy is more common in men about 66.5%.[15] In our research study, we had the data on individual risk factors for epilepsy.

Among 200 epileptic patients the risk factors we observed are Idiopathic were 57.0% (n= 114), Genetic were 33.5% (n= 67) and Age were 9.5% (n=19). There is a higher risk of individuals with unknown cause of epilepsy than those of other age related or Genetic associated risk factor.[13]

The Generalized tonic–clonic seizures were the predominant seizure type overall, encountered about 57% (n= 114). The higher prevalence of generalized tonic–clonic seizures in adults is also reported in a consistent study.[16] In healthy volunteers (n= 200) the cognitive changes of 2.0% (n= 4), Behavioural changes of 5.0% (n= 10) were observed and 93.0% (n=186) were having no change where as in Epileptic patients (n= 200) the cognitive changes of 11.5% (n= 23), Behavioural changes of 19.0% (n= 38), Both C&B changes 5.5% (n= 11) were observed and 64.0% (n=128) were having no change. From the obtained results the cognitive and behavioural effects are significantly increased in epilepsy patients compared to control group.[13]

The level of severity of cognition and behavioural change is mild in healthy volunteers when compared to diseased patients who are on continuous medication. In our study the main objective is to compare the cognitive and behavioural change of Levetiracetam with other antiepileptic drugs. Patients using Sodium valproate, Phenytoin, Carbamazepine, Clobazam and Lamotrigine are the other antiepileptic drugs we had included. Majorly these are the most prescribed AEDSs for Epileptic patients where these drugs are also responsible for cognitive and behavioral changes.[17]

The level of cognition is assessed by using MMSE scale for comparing patients of Levetiracetam and other antiepileptic drugs. The Severity of cognition was more in patients using Levetiracetam 64.2% (n= 9) when compared to other antiepileptic drugs 22.2% (n= 2). The Behavioural changes are more in Levetiracetam group when compared to other antiepileptic drug which are assessed by DSM V. The severity of Anger (n= 3), Depression (n=4), Memory disturbances (n=5) and Repetitive thoughts (n=1) are more severe in patients using Levetiracetam when compared to other antiepileptic drugs usage having mild and moderate changes. Both Cognition and behavioural changes are changes are seen in patients using AEDs (n= 11). The level of severity of both cognitive and behavioural change in patients using Levetiracetam is more when compared to other antiepileptic's.

We use two standardised questionnaire, MMSE and DSM V to assess and compare the cognitive and behavioural changes of Levetiracetam with other antiepileptic drugs. In patients using Levetiracetam (n= 100) the cognitive changes of 14.0% (n= 14), Behavioural changes of 24.0% (n= 10) and both cognitive and behavioural changes of 8.0% (n= 8) and no change 54.0% (n= 54) were observed, where as in patients using other antiepileptic drugs (n= 100) the cognitive changes of 9.0% (n= 9), Behavioural changes of 14.0% (n= 14), Both C&B changes 3.0% (n= 3) were observed and 74.0% (n=74) were having no change. From the obtained results the cognitive and behavioural effects are more in patients using Levetiracetam when compared to the patients using other antiepileptic drugs.[18]

CONCLUSION

The majority of patients with epilepsy become seizure-free with the first prescribed AED in daily clinical practice. In addition to seizure control, the overall effectiveness is also determined by adverse events, which are responsible for approximately one third of treatment failures. Cognitive and behavioural side effects are common among patients with epilepsy those use AEDs for a prolonged period of time. Patients using Levetiracetam are at risk when compared to older AEDs. The findings in our study may serve as preliminary guidelines for clinicians when prescribing AEDs for patients with Epilepsy and considering side effect profiles of AEDs. This can be achieved by either by titrating the dose or by monitoring the cognition and behavioural changes of the patients. As an add- on therapy the epileptic patients can be prescribed with cognitive enhancers i.e., vitamin B supplements (B1, B6, B12), Neurotonic agents.The behavioral changes due to AEDs can be resolved by Behavioral therapy. By this we can overcome the cognitive and behavioral changes that occur with AEDs. By our study we conclude that the Cognitive and behavioural side effects occur more frequently in patients prescribed with Levetiracetam when compared to other antiepileptic drugs. Further studies can be done in detail on individual drugs cognitive and behavioural side effects to minimise the treatment failures.

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