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Research Article

STUDY ON PREVALENCE OF DEPRESSION AND ADVERSE DRUG REACTIONS AMONG SOUTH INDIAN EPILEPTIC PATIENTS

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ABSTRACT

Objectives: To compare the prevalence and intensity of adverse drug reactions (ADR) in patients receiving antiepileptic monotherapy and polytherapy, and to assess the pattern of depression associated with the therapy.

Methods: This is a prospective observational study conducted in neurology outpatient department for a time period of 6 months in a tertiary care hospital, South India. Patients diagnosed as epileptic for more than 6 months and receiving stable doses of antiepileptic drugs (AED) for 3 months were included in the study. Study participants receiving monotherapy and polytherapy were divided into groups. A detailed validated questionnaire was used to assess the incidence and severity of depression and ADRs among the study participants. Mann–Whitney test, Kruskal–Wallis test, and Wilcoxon signed rank test were used to know the statistical significance at $p<0.05$.

Results: Among 91 patients with epilepsy, depression was observed mainly in the study group receiving polytherapy than monotherapy. The severity of ADR observed among various study groups during the first and second visit were compared, which showed that all range of intensity scores were reported. During the second visit, the severity of ADR was high when compared to the first visit. Further incidence of ADRs with AED therapy was compared which showed clinically significant values in all ADRs reported in both monotherapy and polytherapy.

Conclusion: Our study showed, maximum ADRs were among the patients receiving polytherapy, and depression was observed in patients receiving polytherapy. This suggests the need for safe drug practice.

Keywords: Epilepsy, Anti-epileptics, Adverse drug reactions, Depression, Monotherapy, Polytherapy.

INTRODUCTION

Epilepsy is a group of neurological disorders characterized by epileptic seizures [1]. About 1% of people worldwide (65 million) have epilepsy, and nearly 80% of cases occur in developing countries. In 2013, it resulted in 116,000 deaths up from 111,000 deaths in 1990 [2]. It is characterized by a tendency to recurrent seizures and is defined by two or more unprovoked seizures. In approximately 70% of patients with newly diagnosed epilepsy initial treatment with a single antiepileptic drug (AED) leads to complete seizure control without intolerable adverse effects. Unfortunately, monotherapy fails even at maximal tolerated doses in an important minority of patients. These patients usually have symptomatic epilepsies. For patients with refractory seizures, alternative monotherapy with a second-line agent is a very effective and well tolerated treatment policy. Approximately, 40% of patients with partial epilepsy that is refractory to one agent will benefit from alternative monotherapy. If alternative monotherapy fails, polytherapy with a combination of two drugs may be helpful in a small minority of patients. However, this efficacy is usually at the expense of added toxicity unless the daily dose of the first drug is reduced [3].

Although anticonvulsant polytherapy has been widely and traditionally used in the treatment of epilepsy, there is little evidence of its advantages over monotherapy. However, It does leads to problems of chronic toxicity, drug interactions, failure to evaluate individual drugs, and sometimes exacerbation of seizures. There are many causes of polytherapy which could be avoided by more careful monitoring and supervision of therapy [4].

AED treatment is required long-term, and it is potentially hazardous; it is important to choose agents on the basis of their adverse effect profile. Monotherapy in the management of seizure disorder is a laudable goal. Monotherapy typically reduces costs, reduces side effects and improves compliance. It also reduces drug-drug interactions, not only with other AEDs but also with other concomitant medications used in co-morbid illness. CNS side effects tend to be cumulative with centrally acting AEDs and thus adverse effects, such as drowsiness, ataxia, fatigue, or memory difficulties, are lessened with monotherapy [5]. Polytherapy with AEDs is not popular mainly because it is thought to be associated with more adverse effects and contribute relatively little in terms of efficacy compared with monotherapy [6].

Depressive disorders (DDs) are the most common type of psychiatric co-morbidity in patients with epilepsy. The incidence of DDs in epileptics is estimated to be 30-70%. Despite their relatively high prevalence, DDs remain unrecognized and untreated in a large proportion of patients [7]. The decreased activity of serotonin, dopamine, and γ-aminobutyric acid facilitate; the kindling process of seizure foci, worsen seizure frequency and severity, and are reversed or blocked by AEDs. Decreased activities of these neurotransmitters are a pivotal pathogenic mechanism of DDs and form the basis of their pharmacotherapy. Thus, DDs and epilepsy may share common pathogenic mechanisms that facilitate the occurrence of one in the presence of other [7].

At present the undue toxicity, adverse drug reactions (ADRs) and inconvenient interactions are more common in polytherapy. Although monotherapy is universally accepted for treating early epilepsy, as many as 40% of patients will continue to have seizures and develop intolerable adverse effects.

There has been little demonstrable interest in devising systems in the occurrence of adverse events of AEDs in chronic epileptic patients in mono and polytherapy. We collected spontaneous complaints and

compared with a detailed semi-structured questionnaire. It is now widely accepted that the impact of epilepsy on the individual exceeds beyond the occurrence of seizures, and that there is a need for outcome measures sensitive to these consequences [8]. Hence, we measured the current depressive symptomatology and identified possible cases of DDs using the center for epidemiologic studies depression scale (CES-D) in epileptic patients. Furthermore, we assessed whether depression may aggravate the number and intensity of side effects in patients using AEDs. This study was aimed to compare the prevalence and intensity of ADR in patients receiving antiepileptic monotherapy and polytherapy, and to assess the pattern of depression associated with therapy.

METHODS

A prospective observational study was carried out over the duration of 6 months from November, 2014 to April 2015 at Kovai Medical Center and Hospital (KMCH), Coimbatore, Tamil Nadu, India.

This study was approved by Institutional Ethics Committee. The data were collected from various sources such as patient's case reports, treatment charts, and patient's laboratory investigation and also through direct patient interview. The diagnosis of epilepsy was confirmed in every patient by computed tomography and/or magnetic resonance imaging scan reports. Other necessary data such as lab investigations and drugs prescribed were collected. Study participants and their relatives were clearly explained regarding the study and informed consent were collected from them.

The study participants irrespective of their gender diagnosed for epilepsy at least 6 months and receiving stable dose of anti-epileptic drug for at least 3 months were included in the study. The patients below 5 years of age, uncertainty in diagnosis of epilepsy, cognitive impairment, febrile illness, and non-compliant patients were excluded from the study.

To assess the presence and severity of ADRs among the study groups treated with monotherapy and polytherapy during their first and second (after 3-4 months) visit a detailed semi-structured questionnaire was used. Further CES-D questionnaire [9] was used to assess depression status in the study group during their first visit. ADRs of the first and second visit were rated as 1-4 points, according to the scale [10]. The presence of probable depression (score > 15) according to the CES-D was differentiated into three groups according to the score:

a. If the score is 22 or higher, the patient may be suffering from a major depression,
b. If the score is 15-21, the patient may be suffering from mild to moderate depression,
c. If the score is below 15, the test does not indicate that the patient is depressed.

Statistical analysis was performed using Mann–Whitney test, Kruskal–Wallis test and Wilcoxon Signed Rank test to know the level of significance as ($p<0.05$). Questionnaires were validated by using Cronbach α reliability coefficient.

RESULTS

A total of 91 epileptic patients who visited neurology outpatient department of the hospital were included in the study. Among the study population, male (56.04%) population were comparatively high than female (43.96%) population.

Patients treated with AEDs were divided into two groups, one group receiving monotherapy (53.85%) and the other receiving polytherapy (46.15%). Further, the study group was categorized on the basis of the severity of depression, like absent, mild to moderate and major. Among patients treated with monotherapy most of them were without depression, followed by 10 (20.4%) males and 5 (10.2%) females with major depression and few of them 3 (6.12%) males and 4 (8.16%) females had mild to moderate depression. In 49 polytherapy patients, majority of 15 (35.71%) males and 11 (26.19%) females had major depression, followed by few patients without depression while the rest, 4 (9.52%) males and 3 (7.14%) females had mild to moderate depression.

The study group was further compared with the ADR intensity scored during first and second visits. Patients with depression (n=55) in their first visit, the majority of male and female fell in the ADR intensity score of 21-30 and least number had an intensity score of more than 40 (Table 1). During the second visit, it was found that majority of male and female had an intensity score between 31 and 40 and none of them fell in 1-20 categories (Table 2). Patients without depression (n=36), during their first visit majority of males and females had an intensity score between 1 and 20 while none of them fell in 31-40 and more than 40 category (Table 1). In the second visit, majority of 10 (18.18%) males and 9 (25%) females scored between 21 and 30 while none of them fell in more than 40 category of ADR score (Table 2).

In our study, the severity of ADRs during the first visit in monotherapy patients showed those 6 patients with lack of concentration, 4 patients with emotional liability, and 1 patient each in tremor, dizziness and sleep disturbance had more frequent ADRs. Nearly 80% of patients reported absence of ADRs such as aggressiveness, anxiety, hair loss, skin reactions, diplopia, dyspepsia, gingival hypertrophy, somnolence, and memory impairment. Average of 6 and 4 patients reported rare and mild ADRs (Table 3).

Prescription of patients treated with polytherapy was analyzed for drug-drug interactions. Particularly in this group one major drug interaction between valproate and lamotrigine as observed. Nearly, 33% polytherapy patients fell under moderate interactions. All data were analyzed by Kolmogorov–Smirnov test. Since all values were >0.05 (5% level) normality assumption was not met, so non-parametric tests like Mann–Whitney test and Kruskal–Wallis test were used for further analysis of data. Difference in ADRs between first and second visit was compared with sex, age, treatment, and depression. There was no significant difference between the groups at 5% level (Table 4).

Depression level was compared with sex, age and treatment within the study group. No significant difference was found between the sex ratio

Table 1: Study population attributed to ADR according to the intensity score with and without depression during first visit

Intensity score	First visit			
	With depression (n=55)		Without depression (n=36)	
	M (%)	F (%)	M (%)	F (%)
1-20	5 (9.09)	3 (5.45)	13 (36.11)	11 (30.56)
21-30	13 (23.64)	11 (20)	6 (16.67)	6 (16.67)
31-40	12 (21.82)	8 (14.55)	0 (0)	0 (0)
>40	1 (1.82)	2 (3.64)	0 (0)	0 (0)

ADR: Adverse drug reactions

Table 2: Study population attributed to ADR according to the intensity score with and without depression during second visit

Intensity score	Second visit			
	With depression (n=55)		Without depression (n=36)	
	M (%)	F (%)	M (%)	F (%)
1-20	0 (0)	0 (0)	4 (11.11)	5 (13.89)
21-30	10 (18.18)	9 (16.36)	10 (18.18)	9 (25)
31-40	16 (29.09)	9 (16.36)	4 (11.11)	3 (8.33)
>40	5 (9.09)	6 (10.91)	0 (0)	0 (0)

ADR: Adverse drug reactions

Table 3: Severity of ADR on first visit and second visit

ADRs	Number of subjects (n=49)							
	First visit				Second visit			
	Absent	Rare	Mild	Frequent	Absent	Rare	Mild	Frequent
Emotional liability	26	11	8	4	30	7	17	5
Fatigue	38	4	7	0	33	4	7	5
Psychomotor agitation	34	9	6	0	28	8	7	6
Aggressively	46	2	1	0	42	5	1	1
Anxiety	41	5	3	0	28	10	7	4
Headache	36	7	5	0	26	7	12	4
Hair loss	42	5	2	0	39	4	5	1
Skin reactions	41	8	0	0	39	5	5	0
Diplopia or blurred vision	43	6	0	0	43	2	2	2
Dyspepsia	40	6	3	0	34	2	11	2
Gingival hypertrophy	46	1	2	0	45	1	3	0
Tremor	36	6	6	1	32	6	7	4
Weight gain	36	9	4	0	31	4	12	2
Dizziness	31	7	10	1	27	4	10	8
Somnolence	43	1	5	0	40	1	3	5
Memory impairment	40	7	2	0	30	9	6	4
Sleep disturbance	30	11	7	1	27	7	8	7
Lack of concentration	26	11	6	6	20	6	11	12

ADR: Adverse drug reactions

at any age group. However, there was a highly significant difference between monotherapy and polytherapy in their depression level at 1% level (Table 5).

All questions were tested for reliability by using Cronbach "α" reliability coefficient. It was found that $\alpha = 0.9649$ for depression questionnaire and $\alpha = 0.8092$ for ADR questionnaire and the questionnaires were highly reliable. Wilcoxon Signed Rank test was used to compare ADRs. Highly significant difference was found in psychomotor agitation, anxiety and headache and most of the ADRs were significant at 5% level while comparing the first and second visits of patients treated with monotherapy, but there was no significant difference in diplopia and gingival hypertrophy. Further difference between the first and second visit of polytherapy patients were compared which showed a significant difference between most of the ADRs at 5% level, whereas no significant difference in fatigue, gingival hypertrophy, memory impairment and lack of concentration. There was no significant difference between fatigue, aggressiveness, hair loss, skin reactions, diplopia, gingival hypertrophy and somnolence. Remaining all ADRs showed significant difference between the first and second visit of monotherapy patients without depression. While patients with depression showed no significant difference in emotional liability, dyspepsia gingival hypertrophy, tremor, dizziness, somnolence and sleep between their first and second visit. Remaining all the ADRs had significant difference at 5% level.

In this study, differences in ADR's between first and second visit is not showing any statistical significance, whereas depression level compared within the population showed high statistical significance (p=0.013). In comparison of ADR's, such as fatigue, gingival hypertrophy, memory impairment, sleep disturbance, and lack of concentration, are not showing any statistically significant relation to monotherapy and polytherapy.

When compared the ADRs of polytherapy patients without depression between their first and second visit, it was highlighted that only somnolence had a significant difference at 5% level. However, patients with depression showed no significant difference in fatigue, aggressiveness, anxiety, gingival hypertrophy, memory impairment, sleep disturbance, and lack of concentration. All other ADRs showed significant difference during both the visits (Table 6).

DISCUSSION

Choice of the initial AEDs is based on various factors such as age, sex, and type of seizure. Chronic use of AEDs may be associated with several systemic and CNS ADR [11]. Monotherapy in the management of seizure disorders is a laudable goal. Prior studies showed a reduction in drug-drug interaction not only with AEDs but also with other concomitant medications used in co-morbid conditions [5]. Polytherapy with AEDs is not popular mainly because it is thought to be associated with more adverse effects and to contribute relatively little in terms of efficacy compared with monotherapy [6].

Earlier studies on safety of AEDs found that second generation newer AEDs produce rare idiosyncratic reactions [12]. Researchers have noted a higher incidence of depression among patients with epilepsy than the general population or others with chronic conditions such as hypertension and diabetes. For long-time, depression was thought to be

Table 4: Difference in ADRs between first and second visit compared with in the study population

Factors	Groups	Number	p value
Sex	Male	51	0.749
	Female	40	
Age	<13	11	0.514
	13-21	31	
	22-39	27	
	40-59	19	
	60 and above	3	
Treatment	Monotherapy	49	0.784
	Polytherapy	42	
Depression	Without depression	36	0.522
	With depression	55	

ADR: Adverse drug reactions

Table 5: Depression level compared within the study population

Factors	Groups	Number	p value
Sex	Male	51	0.396
	Female	40	
Age	<13	11	0.395
	13-21	31	
	22-39	27	
	40-59	19	
	60 and above	3	
Treatment	Monotherapy	49	0.000**
	Polytherapy	42	

**Highly significant at 1% level

Table 6: Comparison of ADRs with patients treated with monotherapy and polytherapy

ADRs	Monotherapy			Polytherapy		
	Without depression	With depression	Overall	Without depression	With depression	Overall
Emotional liability	0.009*	0.084	0.002*	0.317	0.046*	0.034*
Fatigue	0.785	0.004*	0.012*	1.000	0.157	0.157
Psychomotor agitation	0.034*	0.003*	0.000**	0.317	0.046*	0.025*
Agressivity	0.157	0.046*	0.014*	0.180	0.102	0.038*
Anxiety	0.004*	0.020*	0.000**	0.102	0.059	0.013*
Headache	0.007*	0.007*	0.000**	0.083	0.002*	0.001*
Hair loss	0.180	0.025*	0.011*	1.000	0.046*	0.046*
Skin reactions	0.317	0.014*	0.008*	0.157	0.007*	0.002*
Diplopia or blurred vision	0.317	0.038*	0.084	0.317	0.003*	0.002*
Dyspepsia	0.025*	0.052	0.005*	0.059	0.011*	0.002*
Gingival hypertrophy	1.000	0.414	0.414	0.317	1.000	0.317
Tremor	0.038*	0.102	0.008*	1.000	0.015*	0.015*
Weight gain	0.039*	0.046*	0.005*	1.000	0.004*	0.004*
Dizziness	0.016*	0.145	0.006*	0.180	0.004*	0.002*
Somnolence	0.066	0.317	0.041*	0.038*	0.039*	0.004*
Memory impairment	0.041*	0.008*	0.001*	1.000	1.000	1.000
Sleep disturbance	0.026*	0.238	0.015*	1.000	0.063	0.063*
Lack of concentration	0.024*	0.011*	0.001*	0.317	0.317	0.180

*Significant at 5% level, **Highly significant at 1% level, ADR: Adverse drug reactions

a complication of epilepsy. People with a history of depression have a 3-7 times higher risk of developing epilepsy [7].

Although standard AEDs (first generation) are effective in achieving complete seizure control in the majority of patients, an appreciable proportion is at least in part resistant to conventional pharmacotherapy. The paper reviews strategies to incorporate new AEDs (second generation) into the treatment arsenal for patients with epilepsy [13]. In our study group, we discussed the basis of reasoned polytherapy and some of the possible interactions between AEDs. The drug interactions between AEDs themselves and with other drugs are frequent but not usually of clinical importance [10].

Epileptic seizures and epileptic syndromes have high prevalence and incidence rates affecting all ages and all races of both sexes. It is estimated that 50 million people live with epilepsy, 80% of whom reside in developing countries. AED broadly used today have a number of ADRs including a propensity for drug interactions. Depression is the most common type of psychiatric co-morbidity in patients with epilepsy. The drug interactions between the AEDs themselves are frequent but not usually of clinical importance. ADRs are highly prevalent when a detailed questionnaire is applied. Aggravation of the number and intensity of ADRs have no relationship with depression. By our study the recommendations we put forward are: To inform all patients about ADRs that is not uncommon especially in the first 2 months, to perform controlled studies for elucidating the specific weakness of monotherapy and polytherapy, to assess the strengths of second generation AEDs compared with the first generation and finally to develop a pragmatic approach until evidence-based choice can be made for choosing monotherapy and polytherapy.

CONCLUSION

Once diagnosed, epileptic patients have to take AEDs for almost entire life, thus safety of AED is much questioned. A number of AED is broadly used today and have a number of ADRs in which depression is the most common type of psychiatric co-morbidity in patients with epilepsy. From our study, it is concluded that the level of depression as well as ADR was higher in patients receiving polytherapy than monotherapy. Thus, we recommend that more studies are needed to elucidate the specific weakness of monotherapy and polytherapy, and strengths of second generation AEDs compared with the first generation, All patients has to be informed about ADRs that are not uncommon specially in the first 2 months and a more realistic approach is needed until an evidence-based choice can be made for choosing monotherapy and polytherapy keeping patient safety in mind.

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