

# Profile of patients presenting with seizures as emergencies and immediate noncompliance to antiepileptic medications

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## ABSTRACT

**Introduction:** Seizure is a common manifestation of the many neurological conditions faced by primary care physicians. This study aims to determine the prevalence, etiology, and predictors of immediate noncompliance of adult patients presenting with seizures to the department of emergency (ED). **Materials and Methods:** We conducted this study in the ED of CMC, Vellore from November 2015 to February 2016. Retrospective chart review was used to gather specific data regarding these consecutive cases. **Results:** During the study period, 477 patients presented with seizures. The prevalence of nontrauma seizures in the ED was 2.3% [Figure 1]. The mean age was  $41.4 \pm 17.25$  years. There was a male predominance (63.1%). About 11.7% had active seizures at presentation to the ED and less than a quarter (21.8%) were determined to have status epilepticus. Nearly 41% had new-onset seizures with common etiologies being idiopathic generalized epilepsy (22.6%), metabolic causes (17.9%), acute febrile illnesses (14.42%), and space-occupying lesions (12.3%). Among those with a history of seizures (58.9%), 87.9% were advised regular medications but 58.5% of them were immediately noncompliant. Phenytoin (58.6%), sodium valproate (20.5%), and levetiracetam (18%) were the most commonly used antiepileptics with 23% on multidrug therapy. About 60% were discharged stable from the ED. Univariate analysis showed chronic alcohol consumption (OR: 2.78; 95% CI: 1, 7.7) and female sex (OR: 1.45; 95% CI: 1–2.5) to be predictors of immediate noncompliance to antiepileptics. **Conclusion:** Common etiologies of new-onset seizures in the ED are idiopathic generalized epilepsy, metabolic causes, and acute febrile illnesses. More than half the patients with a known seizure disorder are immediately noncompliant to the advised medications. Knowledge among primary healthcare physicians about the importance of emphasizing compliance will greatly reduce the burden of seizures.

**Keywords:** Compliance, emergency department, etiology, profile, seizures

## Introduction

Seizures are a common presentation of many neurological conditions that are faced by primary healthcare physicians. It is associated with significant morbidity among families, as well as being associated with many superstitious beliefs in the

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population.<sup>[1-2]</sup> The prevalence of epilepsy in low-income and middle-income countries is about twice that of high-income countries.<sup>[1-3]</sup> Less than half of epilepsy cases have an identifiable cause and the etiology of seizures varies from place to place. In the developed world, trauma and space-occupying lesions (SOL) predominate, while the central nervous system (CNS) infections are the main causes of seizures in the developing world.<sup>[4,5]</sup> Antiepileptic drugs (AEDs) are indicated for most cases and need to be taken for many years. Compliance to these medications is a major concern and noncompliance is probably the most common

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cause of recurrent seizures.<sup>[6,7]</sup> Primary care physicians are often the first to prescribe these drugs and counsel patients about compliance with them. The WHO envisages care for epilepsy as a joint effort coordinated between primary and secondary care, with primary care physicians performing the tasks of case finding, adequate referral and follow-up, and secondary care providers delegated the duties of diagnostic and investigative services and instituting interventions.<sup>[8,9]</sup> However, in low- and middle-income countries like India, several barriers exist in implementing such a system. One of the most important of these is a dearth of trained physicians, which in turn defaults the care of epilepsy patients to primary care providers.

Most of the studies on seizures in India have been done on hospital in-patients or on out-patients from neurology or neurosurgery departments, the profile of whom varies significantly from those who present to an emergent primary care setting.<sup>[4,5,10]</sup> There is limited data of the etiology and outcome of seizures presenting to the ED's in India. Hence, we conducted this study in our ED to determine the prevalence and etiology of nontrauma seizures and to determine the predictors of immediate noncompliance to antiepileptics among those prescribed medications earlier.

## Materials and Methods

### Study design

Retrospective cross-sectional.

### Setting

Department of Emergency Medicine of Christian Medical College, Vellore.

### Inclusion criteria

1. Adult patients (Age >15 years)
2. Presented to the emergency department with seizures between November 2015 and April 2016.

### Exclusion criteria

1. Patients aged <15 years
2. Patients with seizures due to acute trauma and pseudo-seizures
3. Missing charts or with inadequate data.

### Variables

Patient data was obtained through the hospital's electronic database. Details of history and physical examination findings and demographic details were recorded on a standard data collection sheet. The variables collected include age, sex, type of seizure, and duration of the seizure.

The variables were defined as follows:

1. Status epilepticus was defined as a continuous seizure lasting more than 30 min or two or more seizures without full recovery of consciousness between any of them.

2. Immediate noncompliance was defined as omitting a single dose of antiepileptic drug within the 24 h period preceding a seizure.
3. Triage priority was categorized as priority 1, 2, and 3 based on the Canadian Triage and Acuity Scale.

### Radiological investigations

Radiological imaging in the form of computerized tomography (CT) or magnetic resonance imaging (MRI) was performed in all patients with new-onset seizures and in some patients with recurrent seizures based on the clinical indication.

### Laboratory tests

All patients were administered intravenous or oral AEDs. Serum levels of AEDs were sent only among those on regular medications.

### Statistical analysis

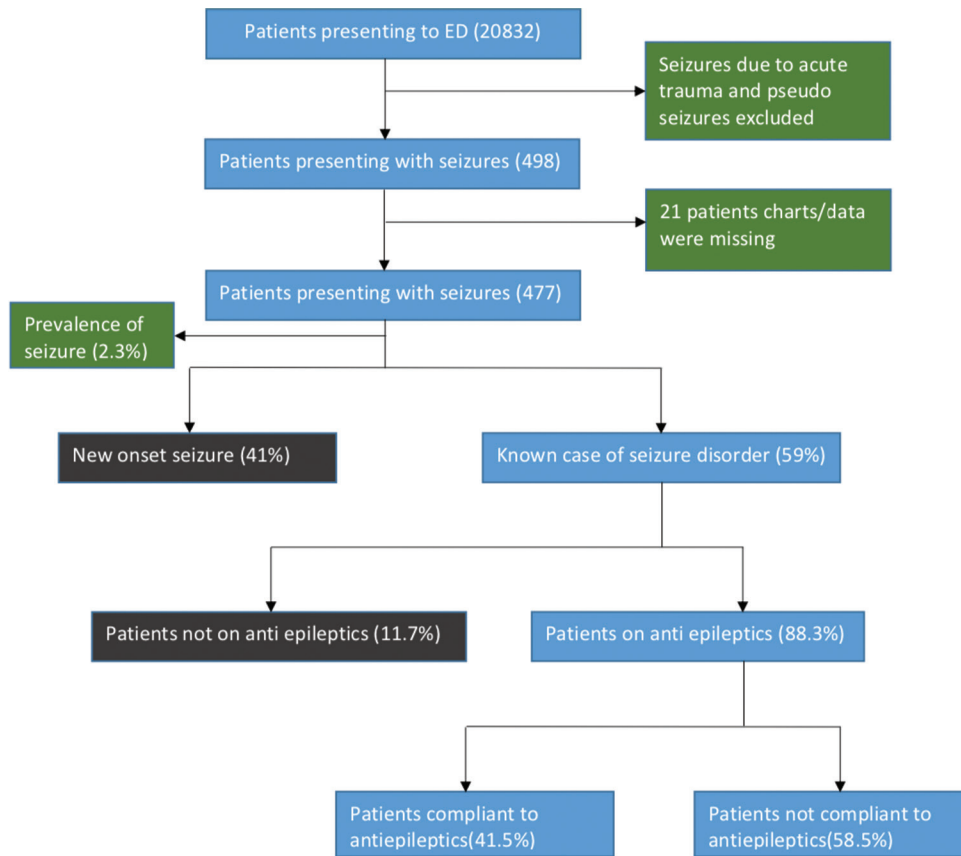
The data was then transferred into the Microsoft excel (version 16) and analyzed using Statistical Package for Social Sciences for Windows (SPSS Inc. Released 2007, version 16.0. Chicago). Continuous variables are presented as mean (standard deviation). Categorical and nominal variables are presented as percentages. Chi-square test or Fisher exact test was used to compare dichotomous variables and *t*-test or Mann-Whitney test was used for continuous variables as appropriate. The predictors of immediate noncompliance was analyzed by univariate analysis and their 95% confidence intervals (CI) were calculated. For all tests, a two-sided *P* < 0.05 was considered statistically significant.

This study was approved by the institutional review board (IRB Min. No. 9986 dated 2<sup>nd</sup> March 2016). Patient confidentiality was maintained using unique identifiers and by password-protected data entry software with restricted users.

## Results

During the study period, 20832 patients presented to the ED. The prevalence of nontrauma seizures was 2.3% (477/20,832) [Figure 1]. The mean age at presentation was  $41.4 \pm 17.25$  years. There was a male predominance (63.1%). The baseline characteristics and clinical presentation are shown in Table 1. Only 11.7% of the patients had active seizures at presentation to the ED. Less than a quarter (21.8%) were determined to have status epilepticus. A majority (80.5%) had generalized tonic-clonic seizures (GTCS) while 17% had focal seizures.

About 41% of the patients had new-onset seizures with common etiologies being idiopathic seizure disorder (22.6%), metabolic causes (17.9%), and acute febrile illness (14.4%) [Table 2]. Metabolic causes included hyponatremia, hypoglycemia, hyperglycemia, and uremia. Among those with a history of seizures, 98% were advised regular medications but 58.5% of them were immediately noncompliant. Phenytoin (58.6%),



**Figure 1:** Strobe statement of patients presenting with seizures

**Table 1: Baseline characteristics (n=477)**

Variable	Number	Percentage
Mean Age (years)	41.4±17.25	-
Males	304	63.7
Diabetes Mellitus	83	17.4
Hypertension	71	14.9
Chronic alcohol consumption	62	13
Past cerebrovascular accident	35	7.3
Triage Priority 1	111	23.2
Triage Priority 2	348	73
Triage Priority 3	18	3.8
Status epilepticus	104	21.8
Actively seizing at presentation	56	11.7
New onset seizures	195	41.1
Patients with known seizure disorder	282	58.9
Patients advised medications for seizures	248/282	87.9
Patients compliant to medications	103/248	41.5
Patients not compliant to medications	145/248	58.4
Multiple drug therapy	56/248	23
Monotherapy	192/248	77
Type of seizure		
Generalized Tonic Clonic Seizure (GTCS)	384	80.5
Focal seizure	81	17
Myoclonic seizure	6	1.25
Absence seizure	6	1.25

sodium valproate (20.5%), and levetiracetam (18%) were the most commonly used antiepileptics with 23% on multidrug therapy.

Among the patients immediately compliant to medications, only 35.6% had serum AEDs levels in the therapeutic range. Univariate analysis showed chronic alcohol consumption (OR: 2.78; 95% CI: 1, 7.7) to be a predictor of immediate noncompliance to antiepileptics. Choice of the antiepileptic, age, sex, and other comorbidities did not have any association with immediate compliance [Table 3].

CT scan of the brain was performed in 46.7% and MRI brain was performed in 20.3% of patients. CT brain was normal in 64% of patients and the radiological findings were shown in Figure 2. More than half (60%) were discharged stable from the ED after controlling the seizures and optimizing antiepileptic dosage.

## Discussion

Our study is one of the few done in the ED setting of a hospital and throws light on the spectrum of etiologies commonly encountered by primary care physicians. The prevalence of seizures (2.3%) is consistent with other studies done in the EDs of the developed world.<sup>[3,6,11,12]</sup> Population-based studies probably have higher and more accurate incidence estimates than hospital-based studies but are more difficult to conduct. Hence, hospital-based prevalence studies like ours is a practical way to understand the burden of a common disease like seizures.

After an extensive evaluation for etiology, almost half of our patients (221 of 477, or 46.3%) were labelled as having idiopathic generalized epilepsy and a quarter (22.6%) of new-onset episodes were idiopathic. The percentage of idiopathic generalized epilepsy is consistent with that reported from the West.<sup>[6]</sup> Indian studies also report etiology as idiopathic in 31–66% of patients.<sup>[13,14]</sup> The percentage of new-onset seizures in the ED as reported by Huff *et al.* was 26% and 62% as reported by Chhabra *et al.*<sup>[6,13]</sup> We noted that 41% of our patients had new-onset seizures.

The definition of status epilepticus has constantly been changing over the last few decades. Until the 1960s, the term was used to define only

persistent generalized clonic seizures. Many forms of status have been recognized by experts thereafter and currently there exist as many types of status epilepticus as there are types of seizures.<sup>[15]</sup> Studies in the past have reported status epilepticus to be present in 3–30% of patients presenting with seizures.<sup>[4,6,13,14]</sup> The 21.8% rate of status epilepticus in our study is comparable to the rate seen in the literature.

Performing imaging studies in patients with seizures is a crucial decision at the primary care level, as a combination of a limited supply of centers that can provide such services and constrained financial resources of patients themselves. Our study found that nearly half of all patients had a CT or MRI scan done, which closely resembles the use of imaging studies elsewhere.<sup>[16]</sup> Almost two-thirds of CT scans were reported normal and did not affect management in any form. Limiting the use of imaging to patients who have acute head trauma, prolonged alteration of consciousness, or focal neurological deficit at the examination may increase the yield of emergent neuroimaging.<sup>[16]</sup>

AEDs are a major treatment consideration for patients with epilepsy with an effective seizure-free period of 3–5 years being the main target. In our study, 59% of the patients who presented with seizures were known epileptics. Therapy with these drugs is started at a low dose and slowly titrated up to the maintenance dose. In addition to metabolic and organic causes, suboptimal drug levels are a major factor in the recurrence of seizures.

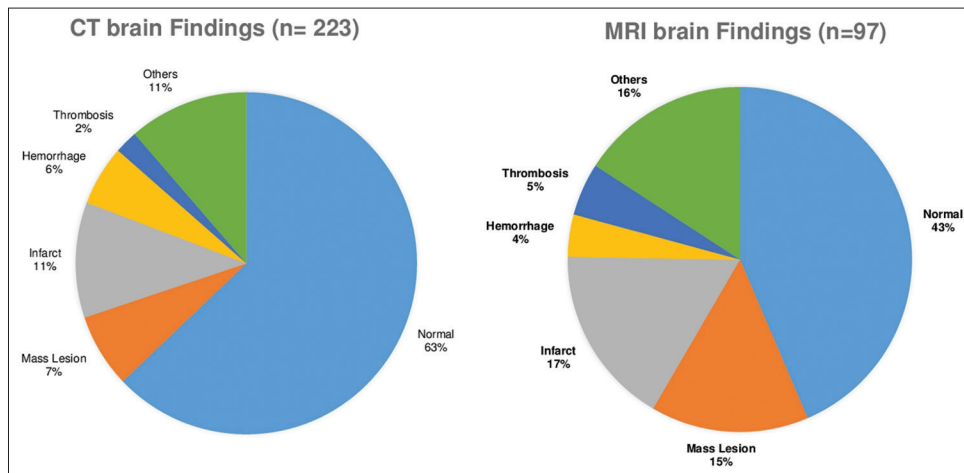
**Table 2: Etiology of new onset seizures (n=195)**

Etiology	Number	Percentage
Idiopathic Generalized Epilepsy	44	22.6%
Metabolic causes	35	17.9%
Acute febrile illness	28	14.4%
Space Occupying Lesion (SOL)	24	12.3%
Cerebrovascular accident	22	11.2%
Alcohol related	14	7.2%
Scar Epilepsy	10	5.1%
Eclampsia	6	3.1%
Others	12	6.2%
Total	195	

Other Causes: Poisoning-5, Drug-induced-4, Autoimmune Encephalitis-1, Vasculitis-1, Wilson's disease-1.  
 Metabolic Causes: Hyponatremia-18, Uremia-9, Hyperglycemia-4, Hypoglycemia-4

**Table 3: Univariate analysis for predictors of immediate noncompliance**

Variable	Immediately Compliant (n=103)	Immediately Noncompliant (n=145)	Odds Ratio (95% CI)	P
Age <65 years	94	137	1.63 (0.6, 4.4)	0.32
Female sex	27	50	1.45 (1, 2.5)	0.18
Chronic Alcohol Consumption	5	18	2.78 (1.1, 7.7)	<0.05
Diabetes Mellitus	8	15	1.37 (0.5, 3.3)	0.5
Hypertension	8	14	1.27 (0.5, 3.1)	0.6
Phenytoin Sodium	46	62	0.61 (0.3, 1.1)	0.11
Sodium Valproate	13	12	0.63 (0.3, 1.5)	0.28
Leviteracetam	11	10	0.64 (0.3, 1.6)	0.35
On Multidrug Therapy	33	23	0.41 (0.2, 0.7)	<0.05



**Figure 2: CT and MRI brain findings**

We found that 58% of known epileptics who were advised AEDs were not immediately compliant, and hence presented with recurrences. Joseph *et al.* from Karnataka, found 90.6% compliance among patients on monotherapy and 75.7% compliance among patients with multiple AED therapy whereas Gurumurthy *et al.* noted a 72.3% rate of compliance.<sup>[14,17]</sup> Dose omissions are common among patients with epilepsy and are reported in up to 71% of patients with 45% of patients reporting a seizure after a missed dose, at some time during the treatment.<sup>[18]</sup> Studies have shown that patients on monotherapy have a higher compliance rate to AED than those on polytherapy (90.6% versus 75.7%).<sup>[19]</sup> Surprisingly, in our study, patients on multiple AEDs were found to be more compliant. We postulate that this is because patients on multiple AEDs were referred to epilepsy clinic multiple times and were more extensively counselled.

Several factors in the community may contribute to the low compliance to medication. While we found chronic alcohol consumption to be a significant predictor of noncompliance, other possible factors include socioeconomic status and even type of seizure.<sup>[17]</sup> Due to the accident and trauma-inducing nature of seizures, which has been known to cause burns, scalds, head and dental injuries, patients' counselling to improve their compliance should be given paramount importance by physicians at all levels.

The development of adequate primary care systems is the need of the hour. Knowledge among primary caregivers, often the first point of contact and counsel of the poor compliance of epileptics to their medications, risk factors for noncompliance, and the serious consequences that follow will reduce the prevalence of seizures. Further steps include the use of home-based approaches, which primary healthcare workers are in a uniquely qualified position to deliver.<sup>[20]</sup>

A developing country like India, where healthcare facilities are few and far between to access, needs to improve its healthcare system, particularly at the primary care level. Increased knowledge among primary healthcare physicians of the common reversible and easily treatable causes of seizures could go a long way in improving its outcome at a community level. It would also help the direct relevant investigation and focused management in resource-strapped settings.

Our study has certain limitations. As it was conducted at a single medical centre, the patient population may be biased by patient selection and referral pattern. Since this study was a retrospective survey, some data was missing. Nonetheless, the study provides useful information about the profile and outcome of patients presenting with seizures to the ED.

## Conclusion

Contrary to the notion among medical professionals that the most common cause of seizures in India is neurocysticercosis; this study suggests that the common etiologies for new-onset seizures in the ED are idiopathic generalized epilepsy, metabolic

causes, acute febrile illnesses, and space-occupying lesions. Awareness of these etiologies will guide management of seizures among primary healthcare physicians. More than half of the patients with a seizure disorder are immediately noncompliant, with several socioeconomic factors at play. Hence effective counseling at first contact is needed to prevent recurrent episodes of seizures and reduce its burden on the community.

## Research quality and ethics statement

The authors of this manuscript declare that this scientific work complies with reporting quality, formatting and reproducibility guidelines set forth by the EQUATOR Network. The authors also attest that this clinical investigation was determined to require Institutional Review Board/Ethics Committee review, and the corresponding protocol/approval number is IRB Min. No. 9986 dated 2<sup>nd</sup> March, 2016. We also certify that we have not plagiarized the contents in this submission and have done a Plagiarism Check.

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Nil.

## Conflicts of interest

There are no conflicts of interest.

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