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ORIGINAL ARTICLE

# Preventable Seizures: A Prospective, Cross Sectional Study On The Influence Of Pharmacological Factors

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## ABSTRACT

The present study was undertaken with an objective to study the extent and pattern of the Pharmacological factors which are responsible for acute seizures reporting at the emergency medicine department of a tertiary care hospital. This prospective and retrospective observational, cross sectional study involved data collection on a specially designed proforma with respect to - seizure diagnosis, duration, co-existing medical conditions, precipitating factors if any, along with details of drug treatment after admission to the emergency ward. Data analysis of 250 patients with a diagnosis of seizures showed a maximum number of males with the highest number of febrile seizures. The evaluation of aetiological factors revealed a maximum number of patients with non-compliance, followed by CNS infections, metabolic and iatrogenic causes and others of unknown aetiology. Interestingly, majority of the patients were from urban background and were educated. The possible pharmacological factors that were identified to have contributed to acute seizures included – lack of appropriate instructions to patients regarding medication intake, in-appropriate dosage of anti-epileptic medication, anti-epileptic drug-drug interactions, in addition to the use of complementary systems of medications, as well as non-compliance. However, though such multiple factors may be considered to have attributed to acute seizures, it may be concluded that a majority of these could be easily controlled and/or can be prevented with simple precautionary measures that have been highlighted under 'conclusions' at the end of this article.

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## Introduction

India has the highest population of people with epilepsy in the world. It is estimated to be approximately 5.5 million with a prevalence rate of 533 per one lakh population [1]. This may be attributed to several causes such as - infectious diseases like tuberculosis of the brain, neurocysticercosis, and malnutrition [2], [3]. Iatrogenic causes may also precipitate seizures which include – inadequate physician advice regarding anti-seizure medications (ASMs) use and/or inappropriate choice and dosage of ASMs, drug interactions between ASMs and drugs administered for concomitant illnesses. Other factors include lack of patient compliance of ASMs and the simultaneous use of alternative systems of medicine [4].

## Objectives

The primary objective of the present study was to identify the pharmacological factors responsible for precipitating seizures and to evaluate the extent and pattern of acute seizures.

## Materials and Methods

All patients diagnosed to have seizures and admitted at the Department of Emergency Medicine, St. John's Medical College Hospital, a tertiary care centre in Bangalore, were included in the study. This was a cross sectional, prospective and retrospective, observational study of one year's duration. The patient information was collected on a specially designed proforma. The patient data was recorded with respect to -

biographical data on - age, sex etc; the disease data - for details with respect to type, frequency, duration of seizure episodes, along with past history and family history of seizures including co-existing illnesses, if any. The details of the medication history for – ASMs used, along with – dose, duration and frequency of their administration, were collected by directly interviewing patients, from their attendants and/or from their medical records. The detailed information on concurrently administered medications with regards to dose, duration of treatment for other illnesses was also recorded.

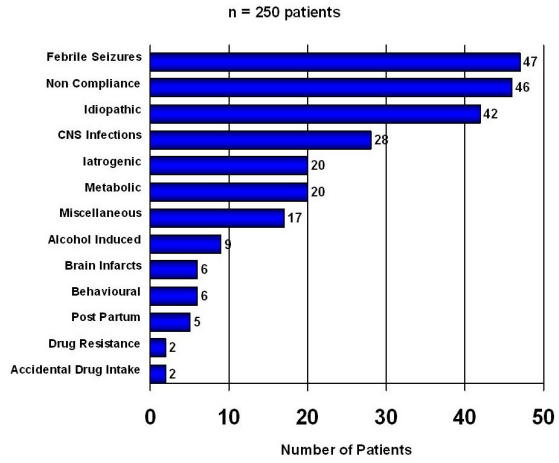
The information thus collected was entered on MS-excel sheets and was analysed using the Lotus Approach Database Management Software with an inbuilt Sequential Query Language. The results are presented after subjecting the data for descriptive analysis.

## Results

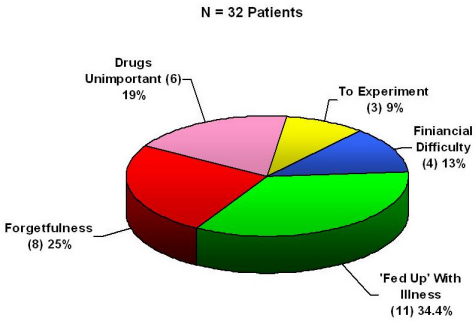
Data from a total of 336 patients with the diagnosis of seizures was collected and recorded over a period of one year of the study. Out of 336 cases, 86 cases (25.60%) were not included in the analysis due to erroneous diagnosis, inability to trace patients or refusal of treatment by the patients. Analysis of the data for gender wise distribution showed a distinct predominance of males (62%) over females (38%), with 92 (37%) cases being treated on an outpatient basis.

Febrile illness (18.80%) was found to be the most common aetiology for seizures, followed by non-compliance (18.40%), Central Nervous System (CNS) infections (11.20%), iatrogenic (8%) and metabolic causes (8%) [Table/Fig 1], while 35.50% cases were of unknown aetiology. 31.90% of cases of febrile seizures were also identified to be cases of non-compliance with ASMs, whereas the remaining patients reported to have seizures for the first time. There were no other factors that could be identified in any of the patients in this latter category which contributed to the incidence of seizures. Non compliance with ASMs was identified in 46 patients (18.40%) and a majority of these were males (73.90%). Surprisingly, most of such patients were from the urban areas and were educated (32, 69.50%). The main reasons for non-compliance ranged from being 'fed up with the illness' (34.40%), to 'a desire to experiment' (9.40%) [Table/Fig 2]. The use of alternative systems of medicine was acknowledged by 10 patients and these were also found to be irregular with their ASM intake. These were hence regarded as being non-compliant to the ASMs prescribed by the allopathic physician. CNS infections included neurocysticercosis (12), meningitis/encephalitis (13) and rickettsial fever (3), which formed 11.20% of the total cases studied. Patients diagnosed to have iatrogenic seizures (20, 18.40%) included - 9 cases with a concomitant treatment for tuberculosis and 1 case on aminophylline for asthma, 4 with insufficient ASM dose, 4 on excessive ASM dose, 1 case of seizure due to withdrawal of ASM on doctor's orders and 1 with seizure following vaccination.

Metabolic causes for seizures accounted for 20 (8%) cases and included diabetes, vomiting, acidosis, alkalosis, hypertension, hypocalcaemia and hyponatraemia. Miscellaneous cases including those with secondary causes such as - head injuries, space occupying lesions (diagnosed by CT scan) and migraine made up 17 (6.80%) of the total cases. Alcohol induced seizures (3.60%), brain infarcts (2.40%), behavioural disturbances (2.40%), pregnancy related seizures (2%), drug resistance (0.80%) and accidental drug ingestion (0.80%) were other causes of seizures.




(Table/Fig 1) Probable Causes of Seizure
n = 250 patients




(Table/Fig 2) Reason for Non-Compliance of ASMs

## Discussion

A number of causes have been reported to precipitate acute seizures, such as – febrile seizures in children [5], CNS infections and metabolic causes [2], [3]. While some seizures are of unknown aetiology, the present study showed ASM non-compliance as well as iatrogenic causes as the second most common cause for seizure precipitation. ASM non-compliance or iatrogenic i.e. seizures caused unintentionally due to - a medical intervention and/or administration of the inappropriate dose of ASM and/or due to co-administration of other drugs leading to seizure precipitation as a result of drug-drug interactions were also reported [6],[7],[8].

Lack of appropriate advice/instructions to patients regarding the consumption of ASMs, coupled with inadequate understanding of pharmacological issues among physicians, have been shown to result in either non-compliance or ASM toxicity [9].

It is well known that compliance plays an important role in controlling seizures as well as in the prevention of their recurrence. Non-compliance was the second most common cause of seizures in our study. The large majority (34.40%) of patients said that they were fed up of using the ASMs and also with the duration of the disease. Other reasons were forgetfulness (25%), a feeling that the drugs were unimportant (18.80%), financial difficulties (12.50%) and a desire to experiment without the drugs (9.40%).

Among those who were non-compliant, some acknowledged the use of alternative systems of medicine, i.e. Ayurveda and Homeopathy. Only limited studies have been carried out on the concomitant use of the Alternative Systems of Medicine with allopathic medication and there is only one study which has examined the interaction between the herbal drug, Shankhapushpi and phenytoin – a commonly used ASM. The results revealed that the levels of phenytoin were reduced by 50% following co-administration of the plant product[4]. It has therefore been recommended to study such interactions systematically and to avoid the use of alternative systems of medicine together with allopathic medication until further research is conducted to evaluate the outcome of their interaction and their concurrent use in therapeutic practice.

It would be expected that with higher education levels, the compliance on the part of the patients would be better. However, in the present study, it was found that 32 patients who were non-compliant were educated and also had an urban background, as against 14 patients whose educational status was not above high school and hailed from a rural background. While 6 patients who were interviewed thought that it was alright to stop taking their drugs, interestingly, 5 of these were males above 30 years of age and had completed their graduation. Such high proportion of non-compliance, even among the educated, suggests that patients are not getting adequate inputs regarding their disease from the medical professionals/community. Since patient compliance leading to better seizure control is well documented [10], [11], it is interesting to note that non-compliance is not necessarily reported from underdeveloped countries, but is also common in the developed world. The importance of patient education programs, therefore, needs to be highlighted. Furthermore, only few studies have shown that such educational programs help to reduce the risk and occurrence of unnecessary seizures[12].

A Nigerian study showed that there was only 25.50% compliance with ASMs after two years of starting treatment [10], while an audit of admissions of patients with seizures to a district

general hospital in the UK demonstrated that poor compliance was a major factor for most admissions among patients with seizure disorders [13]. These studies conclude and suggest that consistent support to these patients would have prevented many of the seizure episodes. Remedying this situation requires the educational intervention with regards to consumption of medications and some knowledge about the disorder, both on the part of doctors as well as the patients.

It is a given understanding in Medicine that both – the medications used and their doses are equally important for the proper control of all medical conditions. Eight patients in our study had seizures due to inappropriate ASM dosage, of which few had received an insufficient ASM dose and hence, had lack of seizure control, while a few were found to have received larger than required doses of ASMs when compared to standard recommended doses. In both groups, there was one case each where a serum drug level was done. The results showed that serum unbound phenytoin levels were lower and above the therapeutic levels, respectively [normal range being – 4-8 μg/L]. The remaining six patients were found to have received a lower or higher dose with reference to their body weight. Manon-Espaillat R, et al. reported an increase in seizure frequency following higher than required doses of ASMs, but the underlying mechanisms are not clearly understood.

Drug-drug interaction is yet another cause for precipitating seizures. Such negative interactions are reported to be either of the dynamic or the kinetic type. There have been several reports including our own on pharmacodynamic antagonistic interactions between xanthines and some of the ASMs in animal seizure models, which showed a decrease in seizure protection by ASMs [15]. Similar Pharmacokinetic interaction studies in humans have shown a decrease in the levels of carbamazepine following the co-administration of caffeine and theophylline [16], [17]. Sporadic reports of seizure precipitation after the consumption of xanthines as beverages or as therapeutic agents have also been reported [18],[19]. The seizurogenic potential of xanthines seen in these studies is attributed primarily to their non-selective adenosine antagonistic activity at the adenosine receptor sites in the CNS, as well as due to their inhibitory effects on the phosphodiesterases, leading to accumulation of CYP-AMP. Pre-clinical studies indicated the possible role of free radicals as the cause for theophylline-induced seizures [20]. In the present study, there were two patients who had received xanthines with ASMs. Although, antagonistic interactions have been reported [18], [19], studies involving a larger number of patients with simultaneous pharmacokinetic and pharmacodynamic [PK-PD] evaluation may help in identifying such antagonistic interactions among patients receiving xanthines with ASMs. Further, careful evaluation of patients with epilepsy receiving xanthine containing bronchodilators for co-existing asthma will be necessary to confirm these results.

In the present study, nine patients were on anti-tuberculosis treatment (ATT). All of them were on isoniazid, which is known to precipitate seizures by decreasing the serum concentration of phenytoin and carbamazepine [8]. However, there is no reported evidence for other anti-tubercular drugs as potential seizurogenic agents.

There is a need to educate and counsel patients by increasing awareness regarding importance of compliance, adverse effects and about drug-drug interactions with ASMs, along with an emphasis on guided ASM monitoring among prescribers.

## Conclusion

There is a need to implement measures to improve drug compliance with ASMs, among patients with epilepsy and to encourage doctors/medical professionals to educate and counsel their patients regarding this. Further, educational and counselling programs may be considered as one of the simple tools relevant to the Indian setting that may be anticipated to help in reducing the incidence of seizures. Additionally, there is a need to study drug-drug interactions between various allopathic drug combinations and between allopathic and alternative systems of medicine. Also, increasing awareness among physicians on beneficial and harmful drug interactions; and the need for appropriate drug dosage will be essential.

The present study supports the view that educational interventions at the 'grass root' level among the various levels of health care professionals, as well as among the public and patients may serve as one of the cost effective measures in preventing preventable seizures.

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