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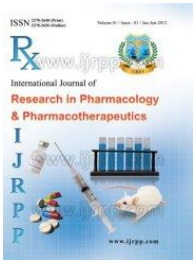

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Comparing the adverse drug reactions of conventional versus newer anti epileptic drugs: an observational study

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ABSTRACT

Introduction

Neurological disorders have been estimated to account for up to 20% of the nationwide cost of healthcare in developed countries. There is growing concern to assess the Adverse Drug Reactions (ADRs) of anti-epileptic drugs (AEDs), which have an impact on compliance, economic burden and quality of life. AEDs have broad spectrum of effects, need long term therapy leading to wide range of ADRs. Thus, the present study was undertaken.

Aim

To assess the incidence, severity, causality of ADRs due to AEDs and to compare the pattern of ADRs caused by conventional versus newer AEDs.

Methodology

This observational study was carried out from 2012 to 2016 to analyze the ADRs reported spontaneously from Department of Neurology at Bangalore Medical College and Research Institute to ADR monitoring centre. Patient demographics, clinical & drug data, details of ADR, onset time, causal drug details, outcome and severity were collected as per CDSCO ADR reporting form. Causality was assessed using WHO-ADR probability scale, preventability by Modified Schumock & Thornton scale and severity using Hartwig and Siegel Scale. Predictability was categorized as Type A and Type B ADRs.

Results

85 ADRs were reported in 5 years, with maximum in 21-40 yrs and equal male to female ratio. Conventional AEDs (75%), mainly Phenytoin (40%) and Carbamazepine (27%) contributed the most. Amongst newer AEDs, Levetiractam accounted for maximum ADRs (13%) followed by Gabapentin (10%). ADRs affecting Central Nervous System (CNS) (65%) were predominant in both groups. Newer AEDs caused Giddiness 10.7 times more frequently than conventional ones. Erythematous rash was 1.71 times more in the conventional drugs than newer ones. Frequency of drug withdrawal was higher among the patients on conventional AEDs (60% vs 30%). Causality assessment indicated that 90% had probable and 10% had possible causality. Majority of the ADRs in both the groups were of moderate severity (50%). The severe ADRs (7%) seen only with conventional AEDs were hepatotoxicity & pancreatitis due to Sodium Valproate and hyponatraemia due to Carbamazepine. Definitely preventable ADRs (12%) were noted among both the groups. No mortality was reported.

Conclusion

85 ADRs due to AEDs were reported in 5 years period. Among conventional AEDs, Phenytoin and Carbamazepine contributed the maximum. Amongst newer AEDs, Levetiractam, followed by Gabapentin were implicated in majority of ADRs. ADRs affecting CNS were predominant in both groups. Severe ADRs were seen with only conventional AEDs.

Keywords: Anti-epileptic drugs, Adverse drug reactions, Causality assessment scale, Severity

INTRODUCTION

World Health Organization (WHO) defines Adverse drug reaction (ADR) as 'any response to a drug which is noxious and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function'. [1] An ADR can lead to significant morbidity, mortality and financial costs. The overall rate of ADRs is estimated to be 6.5%, of which 28% are preventable. In some countries ADR-related costs, such as hospitalization, surgery and lost productivity, exceed the cost of the medications. [2]

Epilepsy is a relatively common condition with no age, racial, social class, geographic or national boundaries and is defined by International League Against Epilepsy (ILAE) as a condition characterised by recurrent epileptic seizures, unprovoked by any immediate identified cause. Approximately 50 million people worldwide suffer from epilepsy and about 10 million are there in India. [3] Epilepsy can influence economic independence through loss of productivity, employment or underemployment due to restrictions on education. [4]

Treatment of epilepsy often imposes an exposure to various anti-epileptic drugs (AEDs) and requires long-term commitment and compliance from the patient. [5] AEDs have a narrow therapeutic index with wide spectrum of ADRs. 10-30% of epileptic patients discontinue their initially prescribed AEDs due to ADRs. [6] These ADRs can be the cause of non-adherence and subjective distress. The newer generation AEDs have reduced adverse events, fewer drug interactions if any and thus improved safety. [7]

Growing public concern over drug safety has stressed the importance of pharmacovigilance, especially in India where ADRs contribute to significant economic burden. [8]. There is growing concern among the healthcare personnel to assess ADRs that has an impact on long term adherence so as to achieve better therapeutic outcome. [9] Pharmacovigilance, the science and activities related to the detection, assessment, understanding and prevention of adverse effects or any drug related problem, is highly essential in India, where there is lack of adequate safety related data for drugs. [10] The drugs available for the treatment of epilepsy have their own unique ADR profile. Therefore, this study was undertaken to study and compare the patterns of ADRs to older and newer AEDs in a tertiary care hospital.

OBJECTIVES

1. To assess the incidence, severity, causality, preventability and predictability of ADRs due to AEDs
2. To compare the pattern of ADRs caused by conventional versus newer AEDs

MATERIALS AND METHODS

An observational study was carried out from January 2012 to May 2016 to analyze the ADRs reported spontaneously from Neurology department, attached to Bangalore Medical College & Research Institute, to Adverse Drug Reaction Monitoring Centre, under Pharmacovigilance Programme of India. Patient's demographics, clinical and drug data, details of ADR, onset time, causal drug details, outcome and severity were collected as per CDSCO form. Causality was assessed using WHO-ADR probability scale, severity using modified Hartwig and Siegel severity scale and preventability using modified Schumock and Thornton scale. Predictability was categorized as Type A and Type B ADRs. The data was analyzed using descriptive statistics to study the characteristics of the ADRs. The conventional AEDs included Phenytoin, Carbamazepine, Phenobarbitone, Sodium valproate and the newer AEDs included Levetiracetam, Lamotrigine,Topiramate and Pregabalin.

RESULTS

A total of 809 ADRs were reported in 5 years, out of which 85 were caused by AEDs. Male to female ratio was 1:1. The age group of 21-40 years was affected the most (42.4%) followed by 41-60 years. [Table 1]

Table 1: Demographic characteristics

AGE (years)	MALE	FEMALE	TOTAL
0-20	6	8	**14**
21-40	16	20	**36**
41-60	11	11	**22**
>60	9	4	**13**
TOTAL	**42**	**43**	

Conventional AEDs contributed to majority of ADRs (75%). Phenytoin (40%) and Carbamazepine (27%) were the commonly implicated conventional AEDs. Amongst newer AEDs, Levetiracetam accounted for maximum ADRs (13%) followed by Gabapentin (10%).

ADRs affecting Central Nervous System (CNS) (65%) were predominant in both the groups followed by cutaneous ADRs [Figure 1]. Newer AEDs caused Giddiness10.7 times more frequently than conventional ones. Erythematous rash was 1.71 times more in the conventional group than newer ones.

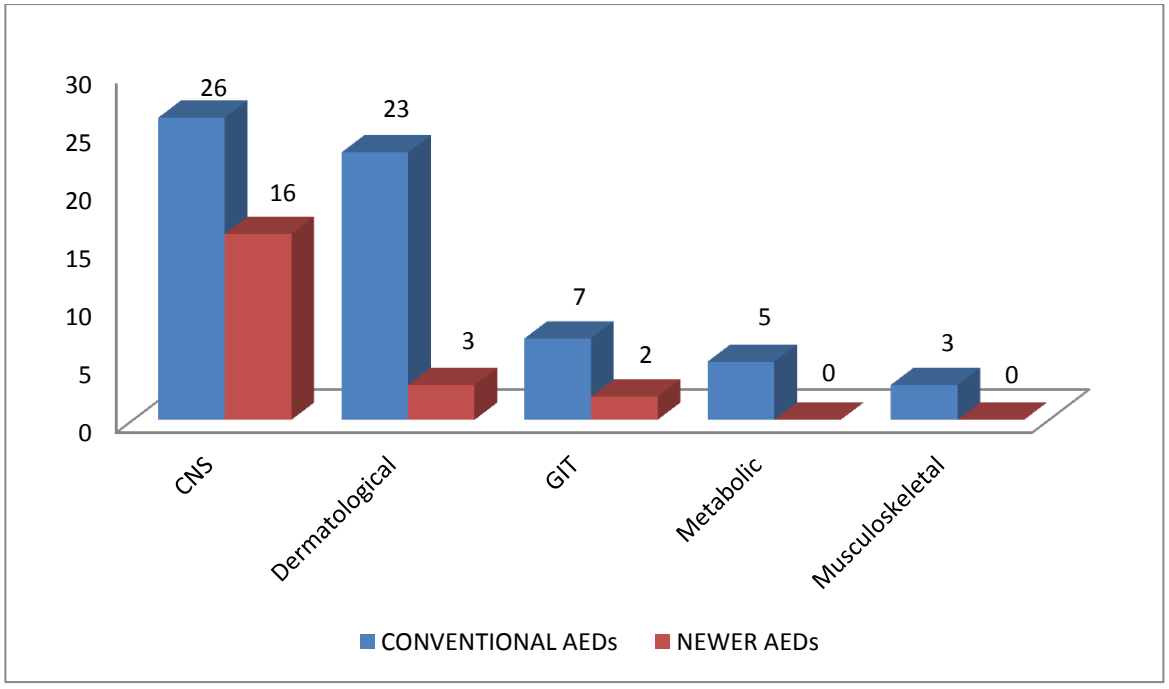

Figure 1: Systems affected by ADRs

Frequency of drug withdrawal was higher among the patients on conventional than those on newer AEDs (44.7% vs12.9%). Dose was reduced in 31.8% of patients whereas in 10.6% cases, there was no change in treatment. [Figure 2]

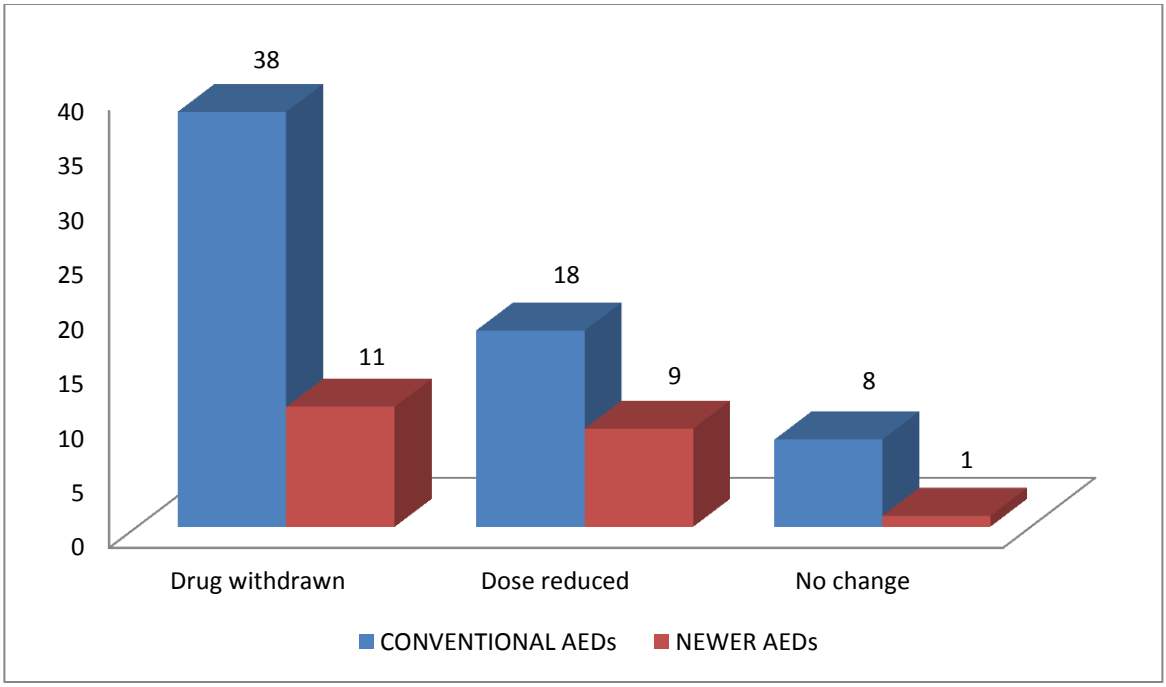

Figure 2: Actions taken for ADRs

Causality assessment indicated that 89.4% had probable and 10.6% had possible causality. [Figure 3] Majority of the ADRs in both the groups were of moderate severity (49.4%) [Figure 4]. The severe ADRs (7%) seen only with conventional AEDs were hepatotoxicity & pancreatitis due to Sodium Valproate and hyponatraemia due to Carbamazepine. According to preventability scale, majority of the ADRs were not preventable (88.2%). [Figure 5]

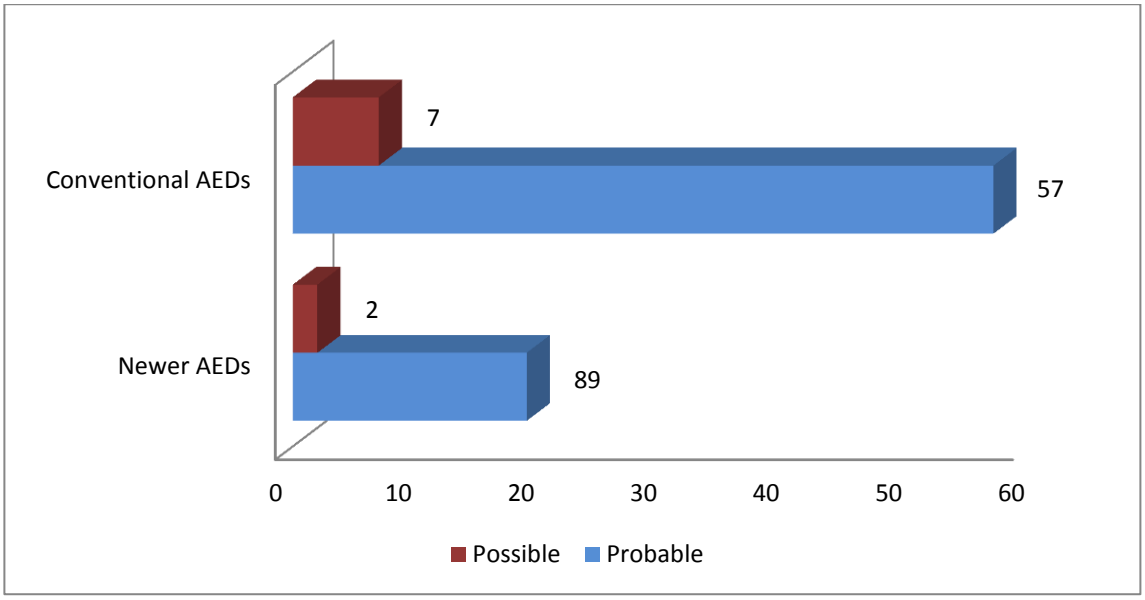

Figure 3: Causality assessment of ADRs

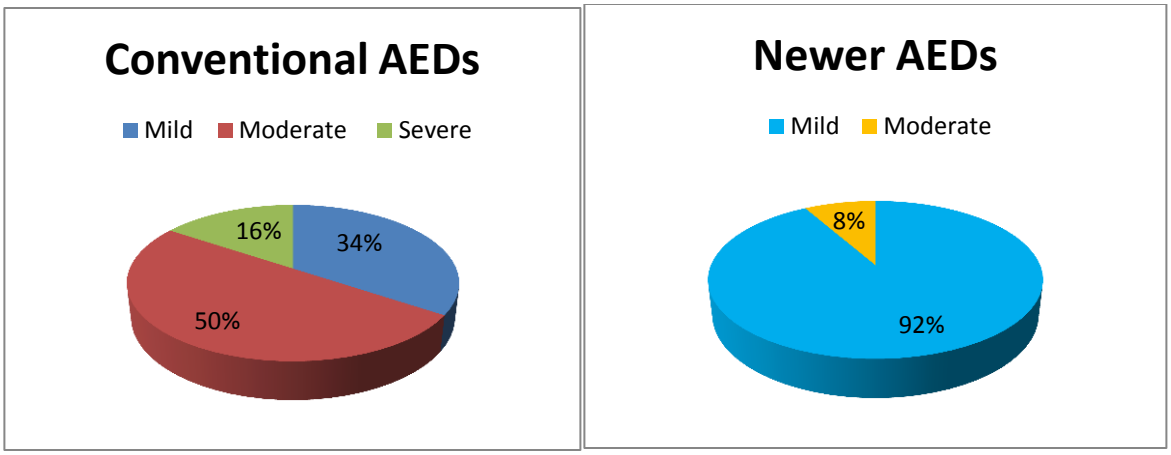

Figure 4: Severity of ADRs

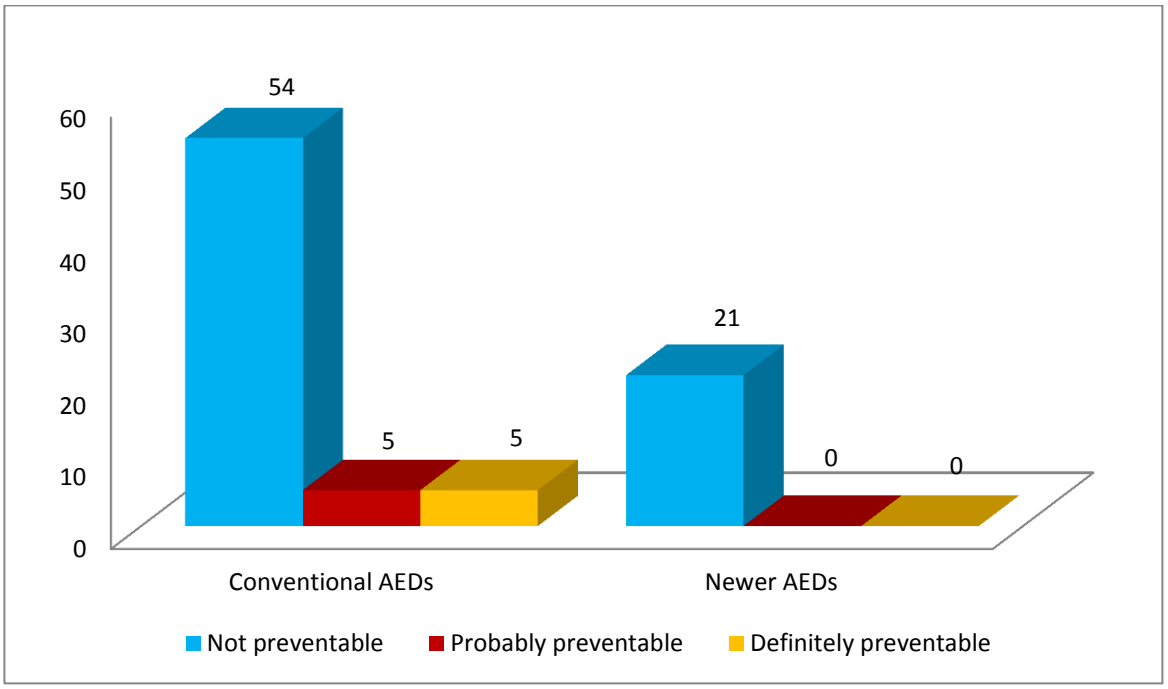

Figure 5: Preventability of ADRs

DISCUSSION

The ultimate goal of epilepsy treatment is to achieve complete seizure control with minimum adverse effects impacting negatively on the quality of life. [6] To address this objective, the present study examined patterns of ADRs reported between the Older versus the Newer AEDs. As ADRs may be experienced very differently by individual patients, AED selection must be individualized. Specific patient characteristics, such as age, gender, concomitant therapies, and concurrent medical and neurologic conditions may increase the likelihood that any given patient will experience adverse event. [11]

A total 809 ADRs were reported, of which 85 were caused by AEDs. The male to female ratio was almost equal [Table 1]. In a study by Gajjar et al in Gujarat, male (68.97%) preponderance was noted while Perucca et al and Pat et al, observed that females were affected more in their study. [6, 12, 13] Majority of the patients were of the age group 21-40 years. [Table 1] Increasing age may enhance the vulnerability of patients to ADRs because of alterations in the pharmacokinetics and

pharmacodyamics of AEDs. [14] However, in the present study, elderly population constituted only 13% of the total. [Table1] This difference may be attributed to the difference in the personality traits in various populations and ages. This finding was similar to the study by Gajjar et al who also reported 18-65 years as the most commonly affected age group. [6]

The most frequently affected system was the Central Nervous System (CNS), and was caused mainly by the conventional AEDs (62%). [Figure1] Since antiepileptic drugs act by modulating the activity of cerebral neurons, the majority of their adverse effects affect the CNS. These effects are often dose-dependent, tend to appear in the early stages of the treatment, can be minimized by gradual dose titration, and few may decrease spontaneously during the course of therapy. These adverse effects vary with the type of drug and its dosage, patient's characteristics and co-medication with specific agents. [15] The increased incidence of CNS effects reported with conventional AEDs may be due to their increased use owing to their low cost, wide availability, long-term experience and once daily dosing. [16] This finding was similar to the study by Jayalekshmi et al who found CNS side effects to be the most common, followed by hepatic and dermatological ADRs. [17]

The second most common ADRs in the present study were cutaneous ADRs caused by conventional AEDs, mainly phenytoin. [Figure 1] In a study by Ghaffarpour et al, it was observed that skin rashes by anti-epileptics are more likely to occur during the first few months of treatment. [18] Few serious ADRs like Stevens Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) were also noted in the present study, caused by phenytoin followed by carbamazepine. A single case of clobazam induced erythema multiforme was also seen. The propensity to develop cutaneous reactions is genetically controlled. [15] Antiepileptic drugs are metabolized to toxic substances in the body that are subsequently detoxified. However due to genetic defect in some individuals, these toxic metabolites may bind to the proteins and trigger an immune response leading to SJS. [19] An association between HLA-B*1502 and SJS induced by carbamazepine and phenytoin has also been shown that is high among patients of Chinese or South East Asian ancestry. Therefore, HLA-B*1502 genotyping is recommended in patients of this ethnic group before starting treatment with one of these drugs. [15]

Two cases of valproate (VPA) induced hepatotoxicity were also noted, that required prolonged hospitalization and was a serious ADR. Hepatotoxic effects of AEDs are well established. According to literature, this form of valproate induced hepatotoxicity is milder, reversible and seems to be dose-dependent, where up to 44% of patients have elevated levels of liver enzymes without clinical symptoms. The pathogenesis of this form of VPA hepatotoxicity is not clear, but is believed to be due to VPA induced impairment of mitochondrial function and fatty acid metabolism. Thus, caution should be taken in the clinical and biochemical monitoring of patients treated with VPA. [20]

ADRs affecting musculoskeletal system were the least common (3.5%), caused only by conventional AEDs. [Figure 1] It may be due to the potential effects of the older-generation AEDs (particularly phenytoin) on bone mineral density. In a study done by Feldkamp et al, proliferation rate of human osteoblast-like cells was found to be increased by phenytoin in low doses. [21] Epilepsy has been shown to increase the risk for fracture by a variety of mechanisms in addition to those attributed to the use of AEDs. The fracture rate in patients with epilepsy is 2–6 times higher than the rate observed in the general population. Hepatic enzyme inducing AEDs such as phenytoin, carbamazepine and phenobarbitone increases the fracture risk more than non-inducing AEDs. [22] Low levels of biologically active vitamin D in patients on AEDs which could be due to metabolism of vitamin D to polar inactive metabolites by the hepatic microsomes have been reported in literature. Another proposed mechanism for the bone effects of AEDs is the inhibition of the cellular response to PTH. [22, 23, 24]

According to WHO causality assessment criteria, majority of the ADRs were probable. [Figure 3] In few cases, the causality was possible, owing to the administration of more than one AED and due to presence of underlying disease. Severity scale indicated only 11.7% to be severe ADRs [Figure 4] that included SJS, pancreatitis, hepatotoxicity, etc. that required intensive care. A large number of mild ADRs were also reported in which the AEDs were not discontinued.

CONCLUSION

85 ADRs due to AEDs were reported in 5 years period. Among conventional AEDs, Phenytoin and carbamazepine contributed the maximum. Amongst newer AEDs, Levetiractam, followed by Gabapentin were implicated in majority of ADRs. ADRs affecting CNS were predominant in both groups. Severe ADRs were seen with only conventional AEDs. Hence, newer AEDs could relatively be safer than conventional ones.

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