Original Research

Comprehensive Surveillance of Adverse Drug Reactions in Antiepileptic Therapy: A Cross-Sectional Analysis at SMHS Hospital, Srinagar

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Abstract

Background: The overarching objective of antiepileptic therapy is to attain optimal seizure control while minimizing the impact of adverse effects. Currently available pharmaceutical interventions for epilepsy treatment exhibit distinctive adverse drug reaction profiles. This study seeks to systematically monitor Adverse Drug Reactions (ADRs) associated with the administration of antiepileptic drugs in individuals with epilepsy.

Methodology: Conducted as a hospital-based cross-sectional investigation, this study was undertaken collaboratively by the Department of Pharmacology and the Department of Medicine at Government Medical College, Srinagar. The analysis focused on patients attending the Neurology Department of SMHS Hospital. Causality and ADR allocation were determined utilizing the Naranjo Monitoring Scale and the WHO-UMC Scale. Severity assessment of ADRs was conducted employing the modified Hart Wig and Siegel Scale (1992).

Results: Phenytoin, valproate, and carbamazepine emerged as the predominant prescriptions, accounting for 31.3%, 23.1%, and 14.2%, respectively. A total of 121 ADRs, encompassing 35 distinct types, were identified in 68 patients, yielding an overall prevalence of approximately 50.7%. Naranjo's Monitoring Scale categorized 73 ADRs (60.3%) as having a 'probable' causal relationship with the antiepileptic drug, while 48 (39.7%) were deemed 'possible.' According to the WHO-UMC Scale, 44 (36.4%) ADRs were classified as 'possible,' 73 (60.3%) as 'probable,' and 4 (3.3%) as 'unlikely.' All reported ADRs were characterized as mild to moderate in severity based on the modified Hart Wig and Siegel Scale.

Conclusion: Healthcare practitioners, particularly those attending to antiepileptic patients, should possess comprehensive knowledge regarding potential ADRs associated with antiepileptic medications. Vigilance is essential for the prevention, management, and alleviation of adverse health effects resulting from ADRs. The establishment of an active pharmacovigilance program is thus imperative for any healthcare institution.

Keywords: Antiepileptic therapy, Drug Reactions, Physicians and other health.

Introduction

Epilepsy stands as a prevalent and enduring neurological disorder characterized by recurrent seizures, emanating from abnormal and excessive synchronous discharges among cerebral neurons, precipitating neurobiological, cognitive, psychological, and social disruptions [1, 2]. A convulsion, defined as a forceful involuntary contraction of skeletal muscles, is a hallmark manifestation of this condition. Epilepsy may manifest post a discernible event, such as asphyxia or head injury, termed symptomatic epilepsy, or may emerge without identifiable cause, denoted as idiopathic epilepsy. Symptomatic epilepsy is occasionally referred to as "secondary epilepsy," contrasting with idiopathic

epilepsy, referred to as "primary epilepsy"; it is pertinent to note that these terms solely apply to seizures and not to epilepsy itself [3]. Globally, over 60 million individuals grapple with epilepsy, constituting 1% of the world's population, with an escalating incidence. Notably, epilepsy impacts 1 in 100 adults and 1 in 20 children, emphasizing its pervasive nature. Reports from the Epilepsy Foundation posit that approximately 1 in 26 individuals across all age groups will confront epilepsy at some juncture, yielding an incidence of around 0.3–0.5% in various populations, with a prevalence rate ranging from five to ten per thousand people [5]. Strikingly, a substantial 80% of these cases are concentrated in developing nations [6], with an estimated 5.5 million individuals affected by epilepsy in India alone [3]. Epilepsy, being a neurological disorder, necessitates immediate medical attention, often entailing prolonged therapeutic interventions. Pharmacotherapy, predominantly comprising antiepileptic drugs (AEDs), constitutes the cornerstone of treatment, achieving complete seizure control in 60% to 95% of patients. The selection of an optimal AED hinges on factors such as accurate epilepsy diagnosis, patient convenience, and the risk of adverse drug reactions (ADRs) [7]. The pharmacotherapeutic arsenal encompasses a plethora of drugs, with conventional options like phenytoin, carbamazepine, valproic acid, and ethosuximide serving as first-line agents due to their cost-effectiveness. Conversely, newer antiepileptics like gabapentin, lamotrigine, vigabatrin, topiramate, tiagabine, and zonisamide are employed as adjuncts or alternatives, prized for their diminished adverse effects and minimal drug interactions [8, 9]. An adverse drug reaction (ADR), defined as a noxious and unintended response to a drug occurring at therapeutic doses, ranks among the foremost contributors to morbidity and mortality, necessitating hospital visits and admissions [11]. Monitoring ADRs is integral to pharmacovigilance (PV), encompassing the detection, assessment, comprehension, and prevention of adverse effects and other drug-related issues [10]. Despite the paramount importance of pharmacovigilance, the ADR profile of psychotropic drugs remains a domain yet to attain the requisite momentum to address the multifaceted challenges faced by a nation grappling with overpopulation, malnutrition, and a high disease burden [12]. A significant stride in this endeavor materialized with the establishment of the National Pharmacovigilance Program in 2005 by India's Drug Control Department within the Ministry of Health and Family Welfare. Originally sponsored by the WHO and funded by the World Bank, the program operated until 2008, subsequently re-emerging as the sustainable Pharmacovigilance Programme of India (PvPI) under the aegis of the Central Drugs Standard Control Organisation (CDSCO) in 2010 [13].

Materials and methods

Upon obtaining ethical approval from the Institutional Ethics Committee, this study was meticulously conducted through the collaborative efforts of the Department of Pharmacology and the Department of Medicine at Government Medical College, Srinagar. The research focus was on patients attending the Neurology Department at SMHS Hospital. Rigorous adherence to ethical considerations was upheld as participants were provided with comprehensive elucidation regarding their inclusion in the study. This elucidation was formalized through the implementation of a Written Informed Consent process, meticulously translated into the local vernacular. The study unfolded as a cross-sectional, observational endeavor spanning a duration of one and a half years.

Inclusion Criteria: All patients, irrespective of gender or age group (above 18 years), who were prescribed anti-epileptic drugs, specifically those grappling with seizures, constituted the primary cohort for this investigation.Adverse Drug Reactions (ADRs) voluntarily documented by attending physicians were also incorporated into the study.

Exclusion Criteria: Patients exhibiting an inability to cooperate were excluded from participation.Individuals incapable of providing informed consent were excluded from the study.Patients relying solely on traditional medicines were excluded.Cases involving drug overdose, whether deliberate or unintentional, were not considered.

Instances of relapse attributed to non-compliance were excluded.Patients experiencing seizures associated with acute conditions such as stroke, or concurrent chronic illnesses like hypertension, diabetes, chronic pulmonary obstructive disease, etc., were excluded.Subsequent to a thorough review of the participants' basic demographic profiles, detailed information was systematically gathered from either the patients or their guardians. This encompassed the duration of illness, number of prior hospitalizations, type and severity of epilepsy, ongoing anti-epileptic treatment, number and names of prescribed drugs, current dosage, treatment duration, and the rationale behind initiating the present treatment (whether it be the first episode or a drug substitution). The evaluation of causality regarding ADRs was conducted employing Naranjo's monitoring scale [14] and the WHO-UMC scale [15]. The severity of ADRs was meticulously assessed using the modified Hart Wig and Siegel Scale [16].Data compilation and analysis were facilitated through Microsoft Excel. Continuous data were succinctly summarized as mean (±) standard

deviation or the five-number summaries, as deemed appropriate. Categorical variables were presented as percentages. The Chi-square test was employed to assess the independence of two categorical variables. Furthermore, graphical representations in the form of bar charts and pie charts were employed to convey a visually informative presentation of the data.

Results

The study population exhibited a mean age of 36.6 years, with a notable majority of 64.9% being male, while the remaining individuals identified as female. The predominant diagnoses within this cohort included idiopathic generalized epilepsy, accounting for 41% of cases, and simple febrile seizures, observed in 22.4% of individuals. These findings underscore the demographic and diagnostic characteristics prevalent within the studied population, providing a foundational understanding of the composition and distribution of the subjects involved in the investigation.

Table-1: Distribution of the study population according to age

Age (years)	Frequency	Percent
< 20 years	2	1.5
21-30 years	39	29.1
31-40 years	51	38.0
41-50 years	32	23.9
51-60 years	8	6.0
61-70 years	2	1.5
Total	134	100.0

Mean 36.6 years, S.D +/- 10.07

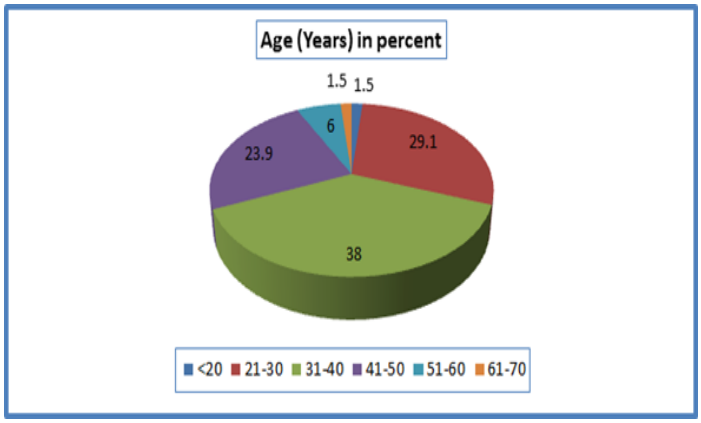
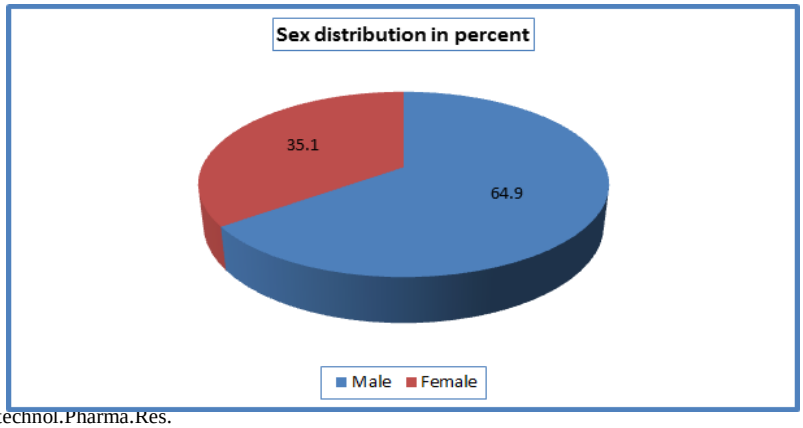


Table-2: Distribution of the study population according to sex

Sex	Frequency	Percent
Male	87	64.9
Female	47	35.1
Total	134	100.0

Phenytoin, valproate, and carbamazepine emerged as the most frequently prescribed medications, encompassing



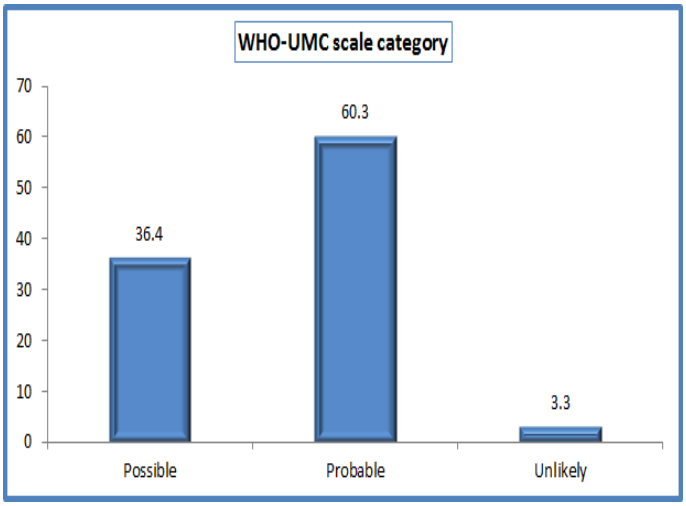
31.3%, 23.1%, and 14.2% of the prescriptions, respectively. Within the studied population, a comprehensive analysis revealed the occurrence of 121 Adverse Drug Reactions (ADRs), spanning 35 distinct types, affecting 68 patients. The overall prevalence of ADRs reached approximately 50.7%. Notably, the causality assessment, conducted using Naranjo's monitoring scale, delineated the relationship between ADRs and antiepileptic drugs. Specifically, 73 ADRs (60.3%) were deemed to have a "probable" causal relationship, while 48 ADRs (39.7%) were categorized as "possible." Further stratification indicated that 36.4% of ADRs were classified as "possible," 60.3% as "probable," and a minimal 3.3% as "unlikely." These findings provide a nuanced understanding of the prevalence, types, and causal relationships associated with Adverse Drug Reactions in the context of antiepileptic drug therapy within the studied cohort.

Table-3: Causality assessment according to Naranjo's monitoring scale

Naranjos score		Frequency	Percent
Doubtful	0	0	0
Possible	1	2	1.7
	2	7	5.8
	3	14	11.6
	4	25	20.7
Probable	5	42	34.7
	6	31	25.6
Total		121	100

Table-4: Causality assessment according to WHO-UMC scale

WHO-UMC scale category	Frequency	Percentage
Possible	44	36.4
Probable	73	60.3
Unlikely	4	3.3
Total	121	100.0



All reported Adverse Drug Reactions (ADRs) within the study were characterized as mild to moderate in severity, as assessed by the modified Hart Wig and Siegel scale. Among the identified ADRs, somnolence emerged as the most prevalent, affecting 14.0% of patients, followed by excessive sedation reported in 9.1% of cases and headache reported in 7.4% of patients. These findings illuminate the predominance of certain ADRs and their respective impact on the well-being of the study participants. The organ systems most frequently implicated in the observed ADRs were neurological, representing 42.1% of cases, followed by gastrointestinal manifestations at 24.8%, and metabolic/endocrine complications at 10.7%. This classification provides insights into the diverse physiological systems affected by the documented adverse reactions, contributing to a comprehensive understanding of their impact. Moreover, a detailed

examination of drug associations revealed that the majority of ADRs were associated with the use of phenytoin, followed by valproate and carbamazepine. This drug-specific attribution sheds light on the varying propensities of antiepileptic medications to elicit specific adverse effects, facilitating a nuanced comprehension of the risk profiles associated with these commonly prescribed drugs in the studied population.

Table-5Frequency of ADRs according to organ system involved

System involved	Frequency	Percentage
Neurological	51	42.1
Metabolic/Endocrine	13	10.7
Gastrointestinal	30	24.8
Skin/Connective Tissue	12	9.9
Autonomic	7	5.8
Others	8	6.6
Total	121	100

Table-6: ADR status in patients according to drugs used

Drugs used	ADR		Total
	Present	Absent	
Phenytoin	24	18	42
Valproate	17	14	31
Carbamazepine	9	10	19
Oxcarbazapeine	4	3	7
Clobazam	4	4	8
Phenobarbitone	3	1	4
Gabapentin	1	0	1
Lamotrigine	2	2	4
Topiramate	1	3	4
Levitracetam	1	4	5
Valproate + Lamotrigine	0	2	2
Valproate + Topiramate	0	2	2
Phenytoin + Gabapentin	1	0	1
Carbamazepine + Leviteracetam	0	2	2
Phenytoin + Lamotrigine	1	1	2
Total	68	66	134

There was no statistically significant relationship between development of ADR with age (p=0.087) or sex (p= 0.957).

Discussion

The predominant demographic composition of the study cohort was characterized by individuals falling within the young and middle-age spectrum, specifically aged between 21 to 50 years, with a mean age calculated at 36.6 years and a standard deviation of ±10.07 years. The gender distribution exhibited a male-to-female ratio of 1.9. A comprehensive statistical scrutiny underscored the absence of a statistically significant relationship between Adverse Drug Reactions (ADRs) and both the age (p=0.087) and gender (p=0.957) of the subjects, aligning cohesively with established findings in the current literature [17-19].In terms of geographical distribution, the residence patterns of the study participants delineated that a substantial 62.7% hailed from rural areas, contrasting with 37.3% residing in urban locales. The overall prevalence of ADRs within this diverse study cohort was reported at 73.1%. A comparative investigation conducted in Erode, Tamil Nadu, by Keerthi Jayalekshmi et al. [20] revealed a lower ADR prevalence of 31.1%, introducing a noteworthy point of contrast. Conversely, a separate survey conducted in Iran documented a considerably higher ADR prevalence of 91.4%, emphasizing the substantial variability in ADR occurrences across different regions and populations. It is pertinent to note that various studies have contributed to the understanding of ADR frequencies following the administration of anti-epileptic drugs, presenting a range from 2.95% to 31.11% [17-20]. This spectrum of reported frequencies underscores the nuanced and multifaceted nature of ADR prevalence in the context of antiepileptic medication usage, with variations likely influenced by diverse patient demographics, healthcare practices, and regional disparities.Of the total 121 reported Adverse Drug Reactions (ADRs), 60.3% were

categorized as having a "probable" causal relationship with antiepileptic drugs based on the Naranjo's monitoring scale, while 39.7% were classified as "possible." Utilizing the WHO-UMC scale, 36.4% were designated as "possible," 60.3% as "probable," and 3.3% as "unlikely." Upon excluding doubtful/unlikely cases, the proportion of causally related ADRs stood at 50.7% (Naranjo's criteria) and 49.2% (WHO-UMC criteria). These observations align with similar findings reported by Prudhivi Ramakrishna et al. [19], where 87.3% of ADRs exhibited a probable causal relationship. Consistent results were also noted in studies by Marc Anderson et al. [18] and Keerthi Jayalekshmi et al. [20]. Notably, our study did not identify any "certain" cases, potentially attributed to the absence of attempted rechallenge with the implicated drug.Regarding diagnoses, idiopathic generalized epilepsy (41%), simple febrile seizures (22.4%), and complex partial seizures (18%) emerged as the three most prevalent conditions within our study. Additional seizure types included symptomatic epilepsy (4.8%), simple partial seizures (11%), and absence seizures (4.8%). These diagnostic distributions mirror findings reported by Shobhana Mathur et al. [17]. The parallel nature of these outcomes underscores the consistency and reliability of diagnostic patterns observed across diverse studies in the field.The predominant pharmaceutical interventions within our study cohort comprised the prescription of phenytoin (31.3%), valproate (23.1%), and carbamazepine (14.1%). Noteworthy is the congruence of these findings with observations reported by Shobhana Mathur et al. [17]. Furthermore, analogous trends have been discerned in parallel investigations conducted by other researchers [18-20]. This convergence in drug prescription patterns suggests a consistent and prevalent approach to pharmacological therapy for epilepsy across multiple studies, reaffirming the robustness and reproducibility of these therapeutic strategies.

Limitation of study: An inherent limitation of this study lies in the relatively modest number of patients enrolled. While our investigation has contributed valuable insights, the sample size may not be comprehensive enough to fully elucidate the spectrum of adverse effects associated with Antiepileptic Drugs (AEDs). Recognizing this constraint, it is imperative to acknowledge the necessity for more expansive research endeavors. Subsequent studies, characterized by larger and more diverse participant cohorts, are warranted to robustly and comprehensively ascertain the adverse effects of AEDs. Only through such expanded investigations can a more thorough understanding of the nuances and potential variations in adverse reactions be achieved, thereby enhancing the generalizability and applicability of findings in the broader context of epilepsy management.

Conclusion

Healthcare professionals, particularly physicians, engaged in the treatment of antiepileptic patients are urged to possess a comprehensive understanding of potential Adverse Drug Reactions (ADRs) associated with antiepileptic medications. Maintaining a vigilant approach is paramount in preventing, addressing, and mitigating the adverse health effects arising from ADRs. To achieve this, the establishment of an active pharmacovigilance program is deemed an indispensable requirement for any health institution. Active engagement in pharmacovigilance endeavors offers valuable insights into the prevailing patterns of ADRs associated with various antiepileptic medications. This proactive approach facilitates the development of strategies to identify and prevent adverse consequences, thereby contributing to an overall enhancement of healthcare delivery for patients with epilepsy. Closely monitoring patients, coupled with timely adjustments in medication doses or, when necessary, the withdrawal of specific drugs, can significantly contribute to the avoidance of ADRs. It is crucial to acknowledge that many antiepileptic drugs exhibit a narrow therapeutic index. Therefore, healthcare providers are encouraged to embrace therapeutic drug monitoring as a routine practice. This ensures not only the effective treatment of epilepsy but also plays a pivotal role in averting potential ADRs. Regular follow-up of patients further solidifies the commitment to providing comprehensive and individualized care, fostering improved treatment outcomes and patient well-being.

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