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Adverse Drug Reactions of Antiepileptic Drugs in the Neurology Department of a Tertiary Care Hospital, Srinagar, Jammu & Kashmir, India

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Abstract

Background: Epilepsy is a disorder that affects 1% of the global population. It is the second most common serious neurologic disorder after stroke, affecting humans. Since antiepileptic drugs have a narrow therapeutic index and their adverse effects can affect any organ, their widespread use has significant safety implications.
Objectives: The study assessed adverse drug reactions (ADRs) using antiepileptic drugs in the Department of Neurology at a Tertiary Care Hospital, Srinagar, Jammu & Kashmir, India.
Methods: This prospective observational study was conducted in the Department of Neurology of a Tertiary Care Hospital, Srinagar, Jammu & Kashmir, India, for eight months. It was a spontaneous reporting of ADRs by practicing physicians in the outpatient and inpatient settings that were included in the study.
Results: Of the 3,300 patients who were on the anti-epileptic drug (AED), 92 (3.07%) had AED-related ADRs. A total of 18 cases were reported in the inpatient department and 74 cases in the outpatient setting. The most common ADRs were loss of appetite (34.78%), skin rashes (17.39%), and gum hypertrophy (9.78%). Of 80 ADRs, 42.5% were related to valproate, followed by phenytoin, carbamazepine, and levetiracetam. The suspected drug was changed in 22 patients with ADRs.
Conclusions: For the early diagnosis and avoidance of ADRs, the frequent follow-up of patients on AEDs is needed to improve patient compliance with drug therapy and provide better drug therapy for avoiding associated morbidity and mortality.

Keywords: Adverse Drug Reactions, Antiepileptic Drug, Epilepsy, Pharmacovigilance

1. Background

Epilepsy is a disorder that affects 1% of the global population. It is the second most common serious neurological disorder after stroke, affecting humans (1, 2). About 50 million individuals have epilepsy worldwide, and 90% of them come from developing nations. It is a widespread progressive neurological condition in which unregulated excitability and recurring unprovoked seizures define the equilibrium between cortical excitability and inhibition (3-6). There is no conclusive indication that the pathophysiology and effects of seizures have distinct distinctions between immature and adult brains. It is a series of multiple types of seizures that differ greatly in severity, appearance, origin, effect, and management (7-9).

Drugs are primary epilepsy treatment, but 60 - 90% of patients with epilepsy can be managed by proper selection and application of antiepileptic drugs (AEDs). The use of an effective seizure control drug depends on seizure diagnosis, patient compliance, and drug side effects, which play an important role in patient compliance (10-15). Since antiepileptic medications have a limited therapeutic index and any organ may be impaired by their adverse effects, their extensive use has substantial safety consequences. Overall, because of intolerance, 10 - 30% of individuals with epilepsy discontinue their originally recommended antiepileptic medicine. The prevalence of adverse effects ranges between 10% and 40% for patients chronically infected with antiepileptic medications. It is also important for optimal clinical practice to consider the manifestations of opioid toxicity, risk factors, and appropriate preventive steps (16, 17).

Pharmacovigilance is important for the safety of public

health because adverse reactions to pharmaceutical drugs for human consumption are avoided, identified, and measured. This includes the administration of pharmaceutical items for human consumption during the life cycle, keeping in view human safety (18-21). As a result, we must highlight the need for pharmacovigilance as continuity and completion of the study of pharmaceutical products starting from clinical trials. The risks posed by the ever-increasing number of drugs, each of which carries an inherent risk of unforeseeable potential for injury, continue to play an important role in resolving them. Whenever adverse effects and toxicity arise, particularly when previously unknown, they must be identified, evaluated, and their importance accurately conveyed to people who know how to perceive the facts (22-27). By ensuring that pharmaceutical products of high consistency, purity, and effectiveness are used rationally, damage can be minimized. We must ensure that the risk of opioid use is expected, well-handled, and conveyed to regulatory agencies and other healthcare providers to accomplish this purpose and increase a sense of trust among patients (28-31). Various Adverse Drug Effects (ADRs) are seen due to the longtime of epilepsy therapy, changing of dosage, and supervision (30, 32-35).

The accuracy and reliability of medication outcome measures are boosted by randomized controlled trials, but specific clinical safety data are not available. Nevertheless, for different ethical, statistical, and practical reasons, the organization of regulated epidemiological practice, which is inclined to provide comprehensive information on ADRs, is exceptionally hard. In India, AED safety monitoring relies primarily on the introduction of the national ADR reporting system, which is a system of spontaneous reporting (SR). However, the challenges of underreporting and flawed data are still hard to address in the SR method. The shortcomings of the SR method may be compensated for by active supervision by physicians, but such study is comparatively lacking. We performed a clinical, observational study to assess ADRs associated with antiepileptic drugs to fill this void. This study focused on the chance of ADR development in patients with epilepsy.

2. Objectives

This study was conducted to assess ADRs arising due to antiepileptic drugs in the Neurology Department of a Tertiary Care Hospital, Srinagar, Jammu & Kashmir, India.

3. Methods

This study was conducted at the Neurology Department of a Tertiary Care Hospital, Srinagar, Jammu & Kashmir, India, for eight months. It was a prospective observational study. Spontaneous reports of ADRs by practicing physicians in the outpatient and inpatient settings of the hospital were included in the study. This study was approved by the Institutional Ethics Committee of the University of Kashmir. The dependent (outcome) variable was the prevalence of ADRs due to antiepileptic drugs. The data interpretation was based on descriptive statistics. The data obtained were presented as mean± Standard Mean Error (SEM) and, where applicable, as percentages. Using MS Excel and SPSS predictive packages of version 20, drug data and patients' characteristics were computed. For the evaluation of the relationship between variables, sufficient statistical tests were used.

4. Results

4.1. Epidemiology of Adverse Drug Reaction

Of 3,300 patients who were on AED therapy during the study period, 92 patients had AED-related ADRs, with a prevalence of 3.07%. Out of 92 patients developing ADRs, 56 were males, and 36 were females. A total of 18 cases were reported in the inpatient department and 74 cases in the outpatient setting. About 51 of the patients visited the hospital due to ADRs, while the rest of 41 patients were detected during their regular follow-ups in the OPD setting. Six age ranges were listed as patients with ADRs. In the age range of 11 - 20 years, the frequency of ADRs was observed to be greater, and the minimum was > 50 years (Table 1).

Table 1. Demographic Characteristics of Study Participants at Neurology Department of a Tertiary Care Hospital, Srinagar, Jammu & Kashmir, 2020

Socio-Demographic Characteristics	Frequency (%)
Sex	
Male	56 (60.9)
Female	36 (39.1)
Age (y)	
< 10	20 (21.7)
11 - 20	21 (22.8)
21 - 30	13 (14.1)
31 - 40	14 (15.2)
41 - 50	13 (14.1)
> 50	11 (11.9)

4.2. Types of Adverse Drug Reactions, Common Drugs, and Management of Adverse Drug Reactions

Antiepileptic drugs used for various neurological disorders can cause different types of ADRs, but the most commonly occurring ADRs were loss of appetite, skin rashes,

gum hypertrophy, tremors, and others (dizziness, weight gain, nausea, vomiting). Out of 80 ADRs, 42.5% were related to valproate, followed by phenytoin, carbamazepine, levetiracetam, and others (pregabalin, oxcarbazepine). The ADRs that occurred in the Neurology Ward were managed using different measures. In 22 patients, therapy with the suspected drug was changed. In 15 patients, the dose of the drug was reduced in therapy with suspected AED (Table 2).

Table 2. Types of Adverse Drug Reaction, Responsible Medications and Management for Adverse Drug Reactions at the Neurology Department of a Tertiary Care Hospital, Srinagar, Jammu & Kashmir, 2020

Variables	No. (%)
Types of adverse drug reaction	
Loss of appetite	32 (34.78)
Skin rash	16 (17.39)
Gum hypertrophy	9 (9.78)
Tremors	9 (9.78)
Nausea and vomiting	06 (6.52)
Abdominal pain	05 (5.43)
Diarrhea	0.3 (3.26)
Stomach pain	0.3 (3.26)
Increase in pulse	0.3 (3.26)
Headache	0.3 (3.26)
Others[a]	0.3 (3.26)
Common drugs	
Carbamazepine	18 (19.56)
Sodium Valproate	38 (41.30)
Phenytoin	21 (22.82)
Levetiracetam	8 (8.69)
Others[b]	7 (7.60)
Measures for management	
Drug changed	22 (23.91)
Dose reduced	15 (16.30)
Doses reduced and another drug added	15 (16.30)
No change	17 (18.47)
No change and other drug added	12 (13.04)
Drug withdrawn	11 (11.95)

[a] Black stool, hot flushes
[b] Clobazam, diazepam, divalproex, ethosuximide, gabapentin, pregabalin, and vigabatrin

4.3. Causality Assessment and Severity Assessment of Adverse Drug Reactions

Causality assessment was done using the Naranjo scale, and according to the score, the ADRs were classified as “definite/highly probable”, “probable”, “possible”, or “unlikely”. Out of 92 ADRs, 42 (45.65%) ADRs were identified as possible, followed by 40 (43.47%) as probable and 10 (10.86%) as definite.

The severity of the patients with ADRs was analyzed using the Hartwig scale (36), and accordingly, they were grouped as "mild", "moderate", or “severe”. Most of the patients were classified as mild (n = 49; 53.26%) and moderate (n = 43; 46.73%) patients. No patients were found to be “severe”. No ADR was recorded that caused permanent harm or led to the death of the patient.

5. Discussion

In this study, the prevalence of ADRs among patients taking AED therapy was below 5%. The study showed that ADRs were most common in the 11 - 20 age group. This result was contrary to the findings from many other studies where children and the elderly were shown to be more prone to developing ADRs (37-39). The low incidence of ADRs among the extreme age groups in our study might be due to the special considerations taken by the practicing physicians in the Neurology Ward concerning prescribing and titrating doses in these vulnerable age groups to prevent avoidable ADRs.

The high number of ADRs reported among 11 - 20 years of age might be due to the changing hormonal milieu in adolescents, which affects the drug metabolism and predisposes ADRs in this age group. In our study, ADRs were found to be more frequent in males (56 patients) than in females (36 patients). Compared to female patients, this might be due to the large number of male patients attending the ward. The most offending drug was found to be sodium valproate, accounting for around 41.30% of the overall prescribed medications that triggered ADRs, followed by the prescription of phenytoin, carbamazepine, and levetiracetam. These findings were in line with previously published studies. (40-43). The most reported ADRs in this study were appetite loss, followed by giddiness/nausea and vomiting. The hepatotoxicity associated with valproate is well known in the literature. The first symptom of irregular functioning of the liver is anorexia. In both, sodium valproate was found to be the offending drug. Phenytoin is the only drug that caused gum hypertrophy, and the majority of the drugs caused skin rashes.

5.1. Conclusions

Still, the prevalence of ADR due to the antiepileptic drug is significant. For the early diagnosis and avoidance of ADRs, frequent follow-ups of patients on AEDs are needed to improve patient compliance with drug therapy and provide better drug therapy for avoiding associated

morbidity and mortality. For this approach to succeed, a "therapeutic alliance" between the patient and clinician is essential. Based on the pharmacology of the AEDs used, medication reactions capable of delivering potentially life-threatening outcomes should be scientifically expected in patients needing AEDs. It can help reduce drug interactions and AEs by reducing polytherapy and choosing AEDs with desirable pharmacokinetic profiles. The tendency to produce these reactions may be affected by various endogenous and environmental influences. The likelihood of early diagnosis and care can be improved by a high degree of suspicion, information about risk factors, and strong physician-patient contact. It is important to thoroughly register and report the diagnosis of serious reactions to the health authorities. The extremely unusual incidence of life-threatening incidents never limits decision-making on care. Future studies into epidemiology, chemistry, and genetics may include methods for assessing which patients are at risk, so excessive exposure should be avoided. The information was beneficial to detect ways to fix issues and also to figure out how to treat patients whenever adverse reactions arise such that the outcomes can be applied to future patient care practices.

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Footnotes

Authors' Contributions: MM and GF conceived the study, designed, participated in data collection, conducted data analysis, and drafted the manuscript for publication. DD assisted in the write-up, analysis, and preparation of the first draft of the manuscript. All authors critically revised the manuscript and approved the final manuscript.

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Informed Consent: The aim and procedure were explained for every patient. Patients signed an informed consent form to participate in the study.

References

1. Stafstrom CE. Epilepsy: a review of selected clinical syndromes and advances in basic science. *J Cereb Blood Flow Metab*. 2006;**26**(8):983–1004. doi: 10.1038/sj.jcbfm.9600265. [PubMed: 16437061].
2. McKeon A, Vaughan C, Delanty N. Seizure versus syncope. *Lancet Neurol*. 2006;**5**(2):171–80. doi: 10.1016/s1474-4422(06)70350-7.
3. Blume WT, Luders HO, Mizrahi E, Tassinari C, van Emde Boas W, Engel JJ. Glossary of descriptive terminology for ictal semiology: report of the ILAE task force on classification and terminology. *Epilepsia*. 2001;**42**(9):1212–8. doi: 10.1046/j.1528-1157.2001.22001.x. [PubMed: 11580774].
4. Kandar HKMCC, Das SK, Ghosh L, Gupta BK. Epilepsy and its management: A review. *Pharma Sci Tech*. 2012;**1**(2):20–6.
5. WHO. *The World Health Report 2001: Mental health: new understanding, new hope*. World Health Organization; 2001. Available from: https://www.who.int/whr/2001/en/.
6. Villanueva V, Sanchez-Alvarez JC, Carreno M, Salas-Puig J, Caballero-Martinez F, Gil-Nagel A. Initiating antiepilepsy treatment: An update of expert consensus in Spain. *Epilepsy Behav*. 2021;**114**(Pt A):107540. doi: 10.1016/j.yebeh.2020.107540. [PubMed: 33243687].
7. Wasterlain CG, Fujikawa DG, Penix L, Sankar R. Pathophysiological mechanisms of brain damage from status epilepticus. *Epilepsia*. 1993;**34 Suppl 1**:S37–53. doi: 10.1111/j.1528-1157.1993.tb05905.x. [PubMed: 8385002].
8. Victor TR, Tsirka SE. Microglial contributions to aberrant neurogenesis and pathophysiology of epilepsy. *Neuroimmunol Neuroinflamm*. 2020;**7**:234–47. doi: 10.20517/2347-8659.2020.02. [PubMed: 33154976]. [PubMed Central: PMC7641338].
9. Jacobs J, Zijlmans M. HFO to measure seizure propensity and improve prognostication in patients with epilepsy. *Epilepsy Curr*. 2020;**20**(6):338–47. doi: 10.1177/1535759720957308. [PubMed: 33081501]. [PubMed Central: PMC7818207].
10. Garnett WR. Optimizing antiepileptic drug therapy in the elderly. *Ann Pharmacother*. 2005;**39**(11):1852–60. doi: 10.1345/aph.1E683. [PubMed: 16189285].
11. Vucicevic K, Miljkovic B, Vezmar S, Todorovic Z, Prostran M, Grabnar I. Population pharmacokinetic analysis of therapeutic drug monitoring data in optimizing pharmacotherapy of antiepileptic drugs. In: Foyaca-Sibat H, editor. *Novel Treatment of Epilepsy*. InTech; 2011. doi: 10.5772/20328.
12. Karimzadeh P, Bakrani V. Antiepileptic drug-related adverse reactions and factors influencing these reactions. *Iran J Child Neurol*. 2013;**7**(3):25–9. [PubMed: 24665302]. [PubMed Central: PMC3943074].
13. Wattanasombat S, Wattanasombat T. Incidence and clinical features of anti-epileptic drug related adverse drug reactions in Chiangrai Prachanukroh Hospital, Thailand. *Thai Pharm Heal Sci*. 2020;**15**(3):176–82.
14. Kulhas Celik I, Dibek Misirlioglu E, Kocabas CN. Recent developments in drug hypersensitivity in children. *Expert Rev Clin Immunol*. 2019;**15**(7):723–33. doi: 10.1080/1744666X.2019.1612241. [PubMed: 31066307].
15. Patel DM, Gurumukhani JK, Patel MV, Patel GR. Phenytoin induced chorea: A rare adverse effect of the drug. *Curr Drug Saf*. 2019;**14**(1):51–2. doi: 10.2174/1574886313666181031161215. [PubMed: 30381086].
16. Jacob S, Nair AB. An updated overview on therapeutic drug monitoring of recent antiepileptic drugs. *Drugs R D*. 2016;**16**(4):303–16. doi: 10.1007/s40268-016-0148-6. [PubMed: 27766590]. [PubMed Central: PMC5114206].
17. Patsalos PN, Spencer EP, Berry DJ. Therapeutic drug monitoring of antiepileptic drugs in epilepsy: A 2018 update. *Ther Drug Monit*. 2018;**40**(5):526–48. doi: 10.1097/FTD.0000000000000546. [PubMed: 29957667].
18. Santoro A, Genov G, Spooner A, Raine J, Arlett P. Promoting and protecting public health: How the european union pharmacovigilance system works. *Drug Saf*. 2017;**40**(10):855–69. doi: 10.1007/s40264-017-0572-8. [PubMed: 28735357]. [PubMed Central: PMC5606958].

19. Kaeding M, Schmälter J, Klika C. *Pharmacovigilance in the European Union: practical implementation across member states*. 1st ed. Springer; 2017.
20. Bhasale AL, Sarpatwari A, De Bruin ML, Lexchin J, Lopert R, Bahri P, et al. Postmarket safety communication for protection of public health: A comparison of regulatory policy in australia, canada, the european union, and the united states. *Clin Pharmacol Ther*. 2020. doi: 10.1002/cpt.2010. [PubMed: 32767557].
21. Geer MI, Gani I, Dar MA, Maqbool M. Insulin resistance and polycystic ovary syndrome: A review. *J drug deliv ther*. 2019;**9**(1-s):433–6. doi: 10.22270/jddt.v9i1-s.2275.
22. Dhikav V, Singh S, Anand KS. Adverse drug reaction monitoring in India. *J Indian Acad Clin Med*. 2004;**5**(1):27–33.
23. Alsfouk BAA, Brodie MJ, Walters M, Kwan P, Chen Z. Tolerability of antiseizure medications in individuals with newly diagnosed epilepsy. *JAMA Neurol*. 2020;**77**(5):574–81. doi: 10.1001/jamaneurol.2020.0032. [PubMed: 32091535]. [PubMed Central: PMC7042855].
24. Jordaan PH. *Pharmacists' perception towards pharmacovigilance and the reporting of adverse drug reactions in South Africa*. North-West University (South-Africa); 2020.
25. Schoedel KA, Szeto I, Setnik B, Sellers EM, Levy-Cooperman N, Mills C, et al. Abuse potential assessment of cannabidiol (CBD) in recreational polydrug users: A randomized, double-blind, controlled trial. *Epilepsy Behav*. 2018;**88**:162–71. doi: 10.1016/j.yebeh.2018.07.027. [PubMed: 30286443].
26. Harmark L, van Grootheest AC. Pharmacovigilance: methods, recent developments and future perspectives. *Eur J Clin Pharmacol*. 2008;**64**(8):743–52. doi: 10.1007/s00228-008-0475-9. [PubMed: 18523760].
27. Meyboom RH, Egberts AC, Gribnau FW, Hekster YA. Pharmacovigilance in perspective. *Drug Saf*. 1999;**21**(6):429–47. doi: 10.2165/00002018-199921060-00001. [PubMed: 10612268].
28. Gawali UP, Bansode AA. Pattern of adverse drug reactions to anti–epileptic drugs in a tertiary care hospital. *Therapy*. 2017;**44**:29.33.
29. Birru EM, Shafi M, Geta M. Drug therapy of epileptic seizures among adult epileptic outpatients of University of Gondar Referral and Teaching Hospital, Gondar, North West Ethiopia. *Neuropsychiatr Dis Treat*. 2016;**12**:3213–9. doi: 10.2147/NDT.S119030. [PubMed: 28053533]. [PubMed Central: PMC5191577].
30. Jayalekshmi K, Palanisamy K, Ramanathan S, Akela S. A study on the adverse drug reactions induced by anti epileptic drugs in the epileptic patients. *J Appl Pharm Sci*. 2016:119–23. doi: 10.7324/japs.2016.60518.
31. Dugassa D, Simegnew D, Melaku G. World journal of advance healthcare research. *World*. 2017;**1**(2).
32. Bulan NVLDT, Magnesium T. *Bab 5 kesimpulan dan saran 5.1 kesimpulan*. 2014. Available from: https://repository.maranatha.edu/12175/7/0651165_Conclusion.pdf.
33. Billakota S, Devinsky O, Kim KW. Why we urgently need improved epilepsy therapies for adult patients. *Neuropharmacology*. 2020;**170**:107855. doi: 10.1016/j.neuropharm.2019.107855. [PubMed: 31751547].
34. Khalil H, Huang C. Adverse drug reactions in primary care: a scoping review. *BMC Health Serv Res*. 2020;**20**(1):5. doi: 10.1186/s12913-019-4651-7. [PubMed: 31902367]. [PubMed Central: PMC6943955].
35. Moavero R, Pisani LR, Pisani F, Curatolo P. Safety and tolerability profile of new antiepileptic drug treatment in children with epilepsy. *Expert Opin Drug Saf*. 2018;**17**(10):1015–28. doi: 10.1080/14740338.2018.1518427. [PubMed: 30169997].
36. Hartwig SC, Siegel J, Schneider PJ. Preventability and severity assessment in reporting adverse drug reactions. *Am J Hosp Pharm*. 1992;**49**(9):2229–32. [PubMed: 1524068].
37. Costa LG, Steardo L, Cuomo V. Structural effects and neurofunctional sequelae of developmental exposure to psychotherapeutic drugs: experimental and clinical aspects. *Pharmacol Rev*. 2004;**56**(1):103–47. doi: 10.1124/pr.56.1.5. [PubMed: 15001664].
38. Sander JW. The use of antiepileptic drugs–principles and practice. *Epilepsia*. 2004;**45 Suppl 6**:28–34. doi: 10.1111/j.0013-9580.2004.455005.x. [PubMed: 15315513].
39. Waterhouse E, Towne A. Seizures in the elderly: Nuances in presentation and treatment. *Cleve Clin J Med*. 2005;**72 Suppl 3**:S26–37. doi: 10.3949/ccjm.72.suppl_3.s26. [PubMed: 16265941].
40. Iorio ML, Moretti U, Colcera S, Magro L, Meneghelli I, Motola D, et al. Use and safety profile of antiepileptic drugs in Italy. *Eur J Clin Pharmacol*. 2007;**63**(4):409–15. doi: 10.1007/s00228-006-0236-6. [PubMed: 17347806].
41. Acharya L, Rao P, Ghosh S. Study and evaluation of the various cutaneous adverse drug reactions in Kasturba hospital, Manipal. *Indian J Pharm Sci*. 2006;**68**(2):212. doi: 10.4103/0250-474x.25717.
42. Noel MV, Sushma M, Guido S. Cutaneous adverse drug reactions in hospitalized patients in a tertiary care center. *Indian J Pharmacol*. 2004;**36**(5):292.
43. Maqbool M, Fekadu G, Dugassa D, Bekele F, Turi E, Simegnew D. The pattern of substance abuse in the psychiatry department of a tertiary care of Srinagar hospital, Jammu and Kashmir, India. *Arch Neurosci*. 2020;**7**(4). doi: 10.5812/ans.106492.