CODEN [USA]: IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES
SJIF Impact Factor: 7.187
https://doi.org/10.5281/zenodo.18523604

Available online at: http://www.iajps.com *Review Article*

A COMPREHENSIVE REVIEW OF REPORTED ADR PATTERN AND GLOBAL SAFETY OF ANTIHYPERTENSIVE DRUGS

Vaishnavi R[1], Bharath Krishna K[2], Thejas H[3], Ayisha Nidha T M[4], Surya Lakshmi R[5], Dr. Sini T Inasu[6], Anupa M Chandran[7]

[6] Associate Professor, Ahalia School of Pharmacy, Ahalia Campus, Kozhippara, Pudussery East, Kerala 678557

[7] Assistant Professor, Ahalia School of Pharmacy, Ahalia Campus, Kozhippara, Pudussery East, Kerala 678557

[1], [2], [3], [4], [5] Students, Ahalia School of Pharmacy, Ahalia Campus, Kozhippara, Pudussery East, Kerala 678557

Abstract:

Adverse drug reactions (ADRs) represent a critical public health burden, with the FDA's Adverse Event Reporting System documenting nearly 175,000 deaths and over 1.25 million major adverse events in 2022. Pharmacovigilance, the systematic detection, assessment, and prevention of ADRs, has evolved from traditional spontaneous reporting systems to incorporate advanced methodologies including electronic health records, real-world data analytics, and artificial intelligence. This article provides a comprehensive review of current pharmacovigilance practices, data sources, and global monitoring systems, with particular emphasis on adverse drug reaction patterns across antihypertensive drug classes—the most frequently prescribed medications for hypertension management. The safety profiles of ACE inhibitors, angiotensin II receptor blockers, calcium channel blockers, diuretics, beta-blockers, and direct vasodilators are examined in detail, highlighting class-specific adverse effects and clinical implications. Additionally, emerging artificial intelligence technologies and their role in enhancing signal detection and pharmacovigilance efficiency are discussed. Continued investment in pharmacovigilance infrastructure, particularly in resource-limited settings, combined with advancement of AI-driven detection systems, is essential for strengthening global drug safety surveillance and improving patient outcomes.

Keywords: *Pharmacovigilance, Adverse drug reactions, Antihypertensive medications, Drug safety, Artificial Intelligence.*

Corresponding author:
Vaishnavi R,
Students, Ahalia School of Pharmacy,
Ahalia Campus, Kozhippara,
Pudussery East, Kerala 678557

QR CODE

Please cite this article in press Vaishnavi R et al., A Comprehensive Review Of Reported Adr Pattern And Global Safety Of Antihypertensive Drugs, Indo Am. J. P. Sci, 2026; 13(01).

INTRODUCTION:

Adverse drug reactions (ADRs) represent a substantial burden on healthcare systems globally. The FDA's Adverse Event Reporting System (FAERS) reported nearly 175,000 deaths and over 1.25 million major adverse events in 2022. For every 1,000 patients, six emergency department visits occur due to pharmaceutical side effects, with 38% resulting in hospitalization. ADRs cause approximately three deaths per 1,000 hospital admissions and significantly increase healthcare costs, morbidity, and mortality (1).

Pharmacovigilance (PV), defined by the World Health Organization as "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem," aims to enhance patient safety through systematic collection, evaluation, and dissemination of drug safety information. PV activities include surveillance of approved medicines and investigational medicinal products to identify unrecognized adverse effects, detect changes in reaction frequency or intensity, and evaluate risk-benefit profiles. Effective communication of safety information to healthcare professionals and patients, along with updated patient information leaflets (PILs), remains essential (2).

Hypertension, the most prevalent cardiovascular condition, affects nearly half of individuals aged 60-70 years, with unknown etiology in approximately 90% of cases. Although 81.5% of people are aware of their condition, only 74.9% receive antihypertensive treatment (3). Poor medication adherence can result in serious consequences including ischaemic heart disease, myocardial infarction, stroke, and end-organ damage such as microalbuminuria and heart failure. Ongoing pharmacovigilance monitoring is essential to assess whether medication benefits continue to outweigh emerging risks (4)(5).

PHARMACOVIGILANCE METHODOLOGIES

Pharmacovigilance now relies on several key methodologies, including spontaneous reporting, cohort and case-control studies in pharmacoepidemiology, active monitoring, and the use of real-world data analytics with electronic health records(EHRs) , big data, and AI(6,7,8). Additional strategies like prescription event monitoring use questionnaires to track patients, while specific registries collect standardized data to generate hypotheses(9,10). EHRs, using natural language processing, enhance detection capabilities, particularly during high-volume events such as pandemics(11).

Spontaneous reporting systems have generated over 30 signal detection algorithms. Advanced statistical methods such as Bayesian models (BCPNN/IC) and techniques including GPS, MGPS, and RGPS offer enhanced specificity while managing multiple testing and confounding. Method selection depends on context: high-sensitivity methods (ROR, PRR, Poisson probability) are ideal for extensive signal detection (6).

DATA SOURCES FOR PHARMACOVIGILANCE

Traditional pharmacovigilance relied primarily on Individual Case Safety Reports (ICSRs) from spontaneous reporting systems. Contemporary practice incorporates diverse data sources including spontaneous reporting databases (FAERS, VigiBase, EudraVigilance, India's PvPI, China's ADR monitoring system), secondary healthcare data (EHRs, insurance claims, hospital data, disease registries), and emerging sources such as patient-generated information, mobile health applications, social media, and pharmacogenomics(6)(7)(12).These are integrated with AI and natural language processing to identify patterns not apparent in structured reports(13)(14).

GLOBAL AND NATIONAL ADR REPORTING SYSTEMS

The World Health Organization oversees international coordination through its Programme for International Drug Monitoring, with VigiBase serving as the global database managed by the Uppsala Monitoring Centre. Over 130 member nations contribute data.(7,12) Regionally and nationally, systems like EudraVigilance in the EU, the US FDA's MedWatch/FAERS, the UK's Yellow Card Scheme, Canada Vigilance, India's Pharmacovigilance Programme (PvPI), and China's national ADR monitoring program are key components.(6,7) These systems support regulatory functions including risk management plans, Risk Evaluation and Mitigation Strategies, Periodic Safety Update Reports, and safety variations, combining spontaneous reporting with active monitoring networks such as the FDA Sentinel Initiative.(7,8)

ADR PATTERNS BY ANTIHYPERTENSIVE DRUG CLASSES

Antihypertensive medications included were Angiotensin Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers, Calcium Channel Blockers, Beta Blockers with the exception of sotalol, thiazide and thiazide-like diuretics, and other antihypertensive, namely methyldopa, moxonidine, prazosin, terazosin, clonidine and hydralazine (42).

Calcium Channel Blockers: Dihydropyridine agents produce selective precapillary arteriolar

dilation with minimal venous effect, causing capillary hydrostatic pressure elevation and peripheral edema. Non-dihydropyridines exhibit distinct profiles with infrequent peripheral edema but prominent negative chronotropic and dromotropic effects, manifesting as bradycardia, atrioventricular conduction disturbances, and constipation(5,15,16,17).

ACE Inhibitors and ARBs: ACE inhibitors consistently demonstrate a persistent, non-productive dry cough—a defining safety signal and leading cause of treatment discontinuation. The cough results from inhibition of ACE enzyme function, preventing bradykinin and substance P degradation, thereby increasing airway sensitivity. Angioedema, though less common, represents a serious adverse reaction with unpredictable temporal occurrence. In contrast, ARBs exhibit markedly lower reporting rates for both cough and angioedema, making them preferable for patients at increased ADR risk.(5,18,19,20,21)

Thiazide and Thiazide-like Diuretics: The dominant safety signal involves metabolic and electrolyte shifts. Hypokalemia is the most frequent abnormality, followed by hyponatremia—particularly concerning in elderly patients who may experience aggressive sodium depletion with serious neurological complications. A strong mechanistic link to hyperuricemia exists due to reduced renal uric acid clearance, frequently triggering gout attacks in susceptible patients (22) (23) (24).

Loop Diuretics: These agents produce aggressive fluid and electrolyte shifts, causing significant hypokalemia, dehydration, and symptomatic hypotension. Unlike thiazides, loop diuretics actively flush calcium and magnesium, leading to hypocalcemia and hypomagnesemia with cardiac and neuromuscular instability risks. Ototoxicity—damage to hearing manifesting as tinnitus or permanent hearing loss—is unique among antihypertensives and increases with high doses, rapid IV administration, and specific agents like ethacrynic acid(25,26).

Centrally Acting Agents: Clonidine carries a notorious "rebound effect" risk: abrupt cessation can cause life-threatening sympathetic overdrive and severe hypertensive crisis. Methyldopa presents rare but serious immune-mediated reactions including hemolytic anemia and liver toxicity, necessitating regular blood monitoring(27,28).

Alpha-Blockers: Orthostatic hypotension is the defining limitation, particularly the "first-dose phenomenon" where a single initial dose (notably prazosin) causes dramatic vascular resistance reduction and syncope. This safety profile has relegated alpha-blockers to secondary status for hypertension treatment, though they remain effective for benign prostatic hyperplasia urinary symptoms.(29,30,31)

Direct Vasodilators: Safety profiles are dominated by compensatory mechanisms. Arterial dilation triggers sympathetic activation, causing tachycardia and reflex sodium and water retention, often necessitating additional medications. Hydralazine carries a unique risk of drug-induced lupus erythematosus (DILE)—an immune-mediated reaction mimicking systemic lupus—typically surfacing after prolonged use. Minoxidil presents cosmetic risks (hypertrichosis) and dangerous cardiac complications (pericardial effusion)(32,33,34).

Beta-Blockers: Safety profiles reflect primary mechanisms: symptomatic bradycardia and atrioventricular conduction delays frequently necessitate dose reduction or discontinuation. Non-selective agents carry significant respiratory risks through unwanted β2-receptor cross-reactivity, triggering bronchospasm in airway disease patients. These drugs dangerously mask autonomic hypoglycemia warning signs (tremors, palpitations) in diabetics(35,36).

Potassium-Sparing Diuretics: Hyperkalemia is the defining limitation, representing a direct adverse effect consequence. Risk increases significantly when combined with RAAS inhibitors (ACEIs or ARBs) or used in renal impairment, potentially creating life-threatening emergencies. Non-aldosterone agents (amiloride, triamterene) avoid hormonal complications but cannot escape the class-wide electrolyte imbalance signature. Vigilant monitoring remains non-negotiable(34,37,38)

CLINICAL IMPLICATIONS AND CURRENT STATUS

The WHO defines ADRs as "any noxious and unintended response to a drug that occurs at doses normally used in humans for prophylaxis, diagnosis, therapy of disease, or modification of physiological function." Major ADRs affect 6.7% of hospitalized patients, making them the fourth to sixth most common cause of death in the US. Studies from Indian tertiary and secondary care hospitals report ADR incidence rates of 1.8-9.8%, with significant proportions classified as severe. ADR-related deaths account for 1.8% of ADR cases and 0.7% of all admissions at some facilities(39).

Most ADRs resolve upon medication cessation or dose reduction, though some cause long-term damage. ADR monitoring remains an ongoing, continuous activity requiring systematic pharmacovigilance approaches (39). Pharmacovigilance development in low-income and middle-income countries (LMICs) progresses slowly, raising concerns about drug safety monitoring infrastructure.(40)

FUTURE DIRECTIONS: ARTIFICIAL INTELLIGENCE IN PHARMACOVIGILANCE

Artificial intelligence significantly enhances pharmacovigilance productivity and accuracy through automation and advanced analytics, addressing limitations of traditional slow and inconsistent approaches. AI applications include automated signal detection, surveillance, and ADR reporting that have substantially improved efficiency. Duplicate detection enhances data precision in safety assessments; data mining and automated signal recognition accelerate safety signal identification. AI improves real-world evidence processing, expanding understanding of therapeutic efficacy and safety while predictive models anticipate ADRs and drug-drug interactions, enabling proactive patient care (41).

Expert-defined Bayesian networks at regional pharmacovigilance centers have optimized causality assessment, reducing subjectivity and processing times from days to hours while increasing medication safety assessment reliability. However, practical AI implementation remains largely limited to academic research due to data quality problems, regulatory obstacles, and demands for more transparent algorithms(41).

CONCLUSION:

Pharmacovigilance represents an essential framework for enhancing drug safety monitoring and patient protection. By integrating traditional spontaneous reporting systems with contemporary methodologies including advanced statistical signal detection, real-world data analytics, and emerging artificial intelligence technologies, healthcare systems can identify previously unrecognized adverse effects and optimize risk-benefit profiles. Systematic monitoring of antihypertensive medications—the most frequently prescribed class in hypertension management—remains critical given their diverse safety profiles across drug classes. Continued investment in pharmacovigilance capacity building, particularly in resource-limited settings, along with advancement of AI-driven detection systems, will strengthen global drug safety surveillance and ultimately improve patient outcomes.

REFERENCES:

1. 1 Kommu S, Carter C, Whitfield P. Adverse drug reactions. InStatPearls [Internet] 2024 Jan 10. StatPearls Publishing.
2. Tiwary P, Vanshika K, Sahu C, Haseena **S.** Review of pharmacovigilance. *World Journal of Pharmaceutical and Life Sciences*. 2022;8(1):40–53.
3. Yadav L, Dutta S, Sharma J, Rai RK, Matreja PS, Pahwa I. A pharmacovigilance study to analyze the adverse drug reactions in patients treated with antihypertensive drug in tertiary care teaching hospitals. J Popul Therapeut Clin Pharmacol. 2024;31(4):1225-33.
4. 4.Agrawal P, Patrick S, Thomas M, Gupta D, Singh Matreja P, Singh P, et al. Pharmacovigilance monitoring and treatment adherence in patients on antihypertensive drugs at a tertiary care centre. Drugs Context. 2024 Oct 21;13:1–10.
5. Hussain A, Aqil M, Alam MS, Khan MR, Kapur P, Pillai KK. A pharmacovigilance study of antihypertensive medicines at a South delhi hospital. Indian journal of pharmaceutical sciences. 2009 May;71(3):338.
6. Jiao XF, Pu L, Lan S, Li H, Zeng L, Wang H, Zhang L. Adverse drug reaction signal detection methods in spontaneous reporting system: a systematic review. Pharmacoepidemiology and Drug Safety. 2024 Mar;33(3):e5768.
7. Wasiullah M, Yadav P, Vishwakarma M, Dubey S, Yadav AK. A comprehensive review of pharmacovigilance: present, past, and future perspectives in patient safety. *Int J Pharm Res Appl*. 2025 Feb;10(2):2520–2528.
8. Zhao Y, Yu Y, Wang H, Li Y, Deng Y, Jiang G, Luo Y. Machine learning in causal inference: application in pharmacovigilance. Drug safety. 2022 May;45(5):459-76.
9. Kumar A, Khan H. Signal detection and their assessment in pharmacovigilance. Open Pharmaceutical Sciences Journal. 2015 Dec 17;2(1).
10. 10 Rani R, Chand S, Singh A, Kumar D, Devi M. A Review on Signal in Pharmacovigilance. Asian Journal of Pharmaceutical research and development. 2019 Dec 15;7(6):80-4.
11. 11 van der Weg W, von Kreijfelt G, Davidson L, Zwaveling J, Visser LE, van Hunsel FP, Kant AC. Strengthening spontaneous reporting-based signal detection during a pandemic with cases from electronic health records using a natural language processing tool. Vaccine. 2025 Aug 30;62:127549.
12. Sunanda S, Prasad SD. Medical Abbreviations Used in Clinical Practice: Common Usage and Standardisation. Journal of Medicine and Health Research. 2025 Aug 21;10(2):171-86.
13. Algarvio RC, Conceição J, Rodrigues PP, Ribeiro I, Ferreira-da-Silva R. Artificial intelligence in pharmacovigilance: a narrative review and practical experience with an expert-defined Bayesian network tool. International Journal of Clinical Pharmacy. 2025 Aug;47(4):932-44.
14. Sarker A, Ginn R, Nikfarjam A, O'Connor K, Smith K, Jayaraman S, Upadhaya T, Gonzalez G. Utilizing social media data for

pharmacovigilance: a review. Journal of biomedical informatics. 2015 Apr 1;54:202-12.
15. Sica DA. Calcium channel blocker-related peripheral edema: can it be resolved?. The Journal of Clinical Hypertension. 2003 Jul;5(4):291-5.
16. Liang L, Kung JY, Mitchelmore B, Cave A, Banh HL. Comparative peripheral edema for dihydropyridines calcium channel blockers treatment: A systematic review and network meta-analysis. The Journal of Clinical Hypertension. 2022 May;24(5):536-54.
17. Handler J. Resistant Hypertension Responding to Change From Furosemide to Thiazide: Understanding Calcium Channel Blocker–Related Edema. The Journal of Clinical Hypertension. 2010 Sep 7;12(12):949.
18. Pinto B, Jadhav U, Singhai P, Sadhanandham S, Shah N. ACEI-induced cough: A review of current evidence and its practical implications for optimal CV risk reduction. Indian Heart Journal. 2020 Sep 1;72(5):345-50.
19. Yilmaz I. Department of Chest Diseases, Division of Immunology and Allergy, Erciyes University School of Medicine, Kayseri, Turkey. Angiotensin-converting enzyme inhibitors induce Cough. Turk. Thorac. J.. 2019;20:36-42.
20. Brown T, Gonzalez J, Monteleone C. Angiotensin-converting enzyme inhibitor–induced angioedema: a review of the literature. The Journal of Clinical Hypertension. 2017 Dec;19(12):1377-82.
21. 21 Jayasinghe M, Caldera D, Prathiraja O, Jena R, Coffie-Pierre JA, Agyei J, Silva MS, Kayani AM, Siddiqui OS, Coffie-Pierre Jr JA, Agyei Sr J. A comprehensive review of bradykinin-induced angioedema versus histamine-induced angioedema in the emergency department. Cureus. 2022 Nov 30;14(11).
22. Yogesh M, Karangia M, Nagda J, Kankhara F, Parmar PA, Shah N. Thiazide diuretics use & risk of falls & syncope among hypertensives: A retrospective cohort study. The Indian Journal of Medical Research. 2025 Feb 14;161(1):99.
23. Jiao XF, Song K, Jiao X, Li H, Zeng L, Zou K, Zhang W, Wang H, Zhang L. Hyperuricaemia, gout and related adverse events associated with antihypertensive drugs: A real-world analysis using the FDA adverse event reporting system. Frontiers in pharmacology. 2023 Jan 9;13:1045561.
24. Di Fulvio M, Rathod YD, Khader S. Diuretics: a review of the pharmacology and effects on glucose homeostasis. Frontiers in Pharmacology. 2025 Mar 28;16:1513125.
25. Lal M, Sahoo PK, Tiwaskar M, Nisty N, Golwala S, Banerjee S, Krishna R, Mehta A, Kumar A, Garg10 N, Arumugam11 G. Unique Pharmacological Properties and Safety Profiles of Loop Diuretics. The Journal of the Association of Physicians of India. 2024 Sep;72(9S):16-8.
26. Xue Z, Liu X, Liu Q, Yang X, Yu L. A disproportionality analysis of adverse events associated with loop diuretics in the FDA Adverse Event Reporting System (FAERS). BMC Pharmacology and Toxicology. 2025 Mar 17;26(1):63.
27. Utuama O, Fasuyi O, Strayhorn G, Booker KL. Methyldopa hepatotoxicity: a paradoxical high-risk pregnancy. Journal of Clinical Gynecology and Obstetrics. 2015 Sep 3;4(3):271-4.
28. Chajai I, El Hernoussi Z, Bentalha A, Kettani S. Rebound hypertension after clonidine withdrawal in a pediatric intensive care unit: a case report. *Int J Adv Res* [Internet]. 2025 May 31 [cited 2026 Jan 4];13(5):860–863.
29. Nachawati D, Leslie SW, Patel JB. Alpha-Blockers. InStatPearls [Internet] 2025 Feb 6. StatPearls Publishing.
30. Zekraoui O, Bhojani N, Zorn KC, Elterman D, Chughtai B. Management and treatment of benign prostatic hyperplasia symptoms: current insights. Research and Reports in Urology. 2025 Dec 31:401-20.
31. Welsh TJ, Mitchell A. Centrally acting antihypertensives and alpha-blockers in people at risk of falls: therapeutic dilemmas—a clinical review. European geriatric medicine. 2023 Aug;14(4):675-82.
32. Nakarmi P, Hermiz J, Vempati R, Chandna S, Bhagat U, Loree S, Gahona CT. Cardiac tamponade due to minoxidil use: a case report and review of the literature. European Journal of Case Reports in Internal Medicine. 2025 May 6;12(6):005379.
33. Solhjoo M, Goyal A, Saliba F, Chauhan K. Drug-Induced Lupus Erythematosus. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. [Updated 2023 Apr 3; cited 2026 Jan 29]..
34. Hariri L, Patel JB. Vasodilators. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. [Updated 2023 Aug 14; cited 2026 Jan 29].
35. Farzam K, Jan A. Beta Blockers. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. [Updated 2023 Aug 22; cited 2026 Jan 29]..
36. Eddin LE, Preyra R, Ahmadi F, Jafari A, Omrani MA, Muanda FT. β-Blockers and risk of neuropsychiatric disorders: A systematic review and meta-analysis. British Journal of Clinical Pharmacology. 2025 Feb;91(2):325-37.
37. Arumugham VB, Shahin MH. Therapeutic Uses of Diuretic Agents. StatPearls.

38. Sun Q, Sever P. Amiloride: A review. Journal of the Renin-Angiotensin-Aldosterone System. 2020 Nov;21(4):1470320320975893.
39. Khurshid F, Aqil M, Alam MS, Kapur P, Pillai KK. Monitoring of adverse drug reactions associated with antihypertensive medicines at a university teaching hospital in New Delhi. DARU J Pharm Sci. 2012 Dec;20(1):34.
40. Menang O, Kuemmerle A, Maigetter K, Burri C. Strategies and interventions to strengthen pharmacovigilance systems in low-income and middle-income countries: a scoping review. BMJ open. 2023 Sep 1;13(9):e071079.
41. Algarvio RC, Conceição J, Rodrigues PP, Ribeiro I, Ferreira-da-Silva R. Artificial intelligence in pharmacovigilance: a narrative review and practical experience with an expert-defined Bayesian network tool. International Journal of Clinical Pharmacy. 2025 Aug;47(4):932-44.
42. Alhawassi TM, Krass I, Pont LG. Antihypertensive-related adverse drug reactions among older hospitalized adults. International Journal of Clinical Pharmacy. 2018 Apr;40(2):428-35.