Available online at *www.ujpronline.com*
Universal Journal of Pharmaceutical Research
An International Peer Reviewed Journal
ISSN: 2831-5235 (Print); 2456-8058 (Electronic)

REVIEW ARTICLE

PHARMACOVIGILANCE ASSESSMENT OF DRUG-INDUCED BARORECEPTOR DYSFUNCTION AND ITS CONTRIBUTION TO CARDIOVASCULAR ADVERSE DRUG REACTIONS

Said Salim Said[1], Burhani Simai[1], Ahmad Makame Mwadini[1], Sabra Salim Rashid[2]

[1]*Zanzibar Food and Drug Agency (ZFDA), Zanzibar, Tanzania.*
[2]*Medicine Policy Unit, Ministry of Health, Zanzibar, Tanzania.*

Article Info:

Article History:
Received: 8 October 2025
Reviewed: 11 November 2025
Accepted: 20 December 2025
Published: 15 January 2026

Cite this article:
Said SS, Simai B, Mwadini AM, Rashid SS. Pharmacovigilance assessment of drug-induced baroreceptor dysfunction and its contribution to cardio-vascular adverse drug reactions. Universal Journal of Pharmaceutical Research 2025; 10(6): 94-97.
http://doi.org/10.22270/ujpr.v10i6.1467

***Address for Correspondence:**
Said Salim, Zanzibar Food and Drug Agency (ZFDA), Zanzibar, Tanzania. Tel: +255-777594373. E-mail: *saidalriyamy67@gmail.com*

Abstract

Drug-induced baroreceptor dysfunction represents an underrecognized mechanism contributing to cardiovascular adverse drug reactions, including reflex tachycardia, bradycardia, syncope, orthostatic hypotension, and arrhythmias. However, despite the critical role played by the baroreflex arc in short-term blood pressure regulation through rapid autonomic adjustments, pharmacological impairment of this reflex has not been systematically evaluated in pharmacovigilance systems. This review synthesizes the current evidence on drug-induced baroreceptor dysfunction, discusses the limitations of spontaneous reporting databases, identifies potential pharmacovigilance signal detection methods, and points out major gaps in current knowledge. It also discusses opportunities opened by emerging tools, such as digital health technologies, computational modelling, and real-world evidence to strengthen the early detection of baroreflex related cardiovascular ADRs. We conclude that integrating baroreceptor-specific endpoints into pharmacovigilance frameworks might improve the prediction, detection, and prevention of serious cardiovascular drug reactions.

Keywords: Blood pressure, baroreceptor dysfunction, cardiovascular adverse drug reactions, pharmacovigilance.

INTRODUCTION

The baroreflex represents the principal short-term regulatory mechanism maintaining beat-to-beat stability of arterial blood pressure[1]. Baroreceptors in the aortic arch and carotid sinus detect variations in arterial strain and provide afferent signals to the nucleus tractussolitarius through the glossopharyngeal and vagus nerves[2]. The efferent response modulates sympathetic and parasympathetic outflow, thereby altering heart rate, myocardial contractility, and vascular tone[3]. Baroreflex sensitivity is a quantitative measure of autonomic cardiovascular regulation and a biomarker of cardiovascular risk[4]. Many pharmacological agents may modulate baroreceptor function by altering receptor stretch sensitivity, impairing afferent signalling, modifying central autonomic integration, or impacting efferent autonomic output[5]. Drugs such as vasodilators, antihypertensive, opioids, antiarrhythmic, psycho-tropic, antipsychotics, anticholinergics, and anaesthetic agents have been implicated in reflex tachycardia, bradycardia, syncope, orthostatic hypotension, and arrhythmogenic events that are mechanistically linked to baroreflex disruption[6]. This mechanism of action, however, remains poorly recognized in clinical practice and poorly documented in the pharmacovigilance systems[7]. Cardiovascular ADRs are one of the major challenges in public health and are also a leading cause of drug withdrawals, black-box warnings, and post-marketing regulatory actions[8]. Despite having important clinical and regulatory implications, baroreflex-mediated adverse drug reactions (ADRs) receive far less attention than drug-induced QT prolongation, torsades de pointes, and ventricular arrhythmias. Despite having important clinical and regulatory implications, baroreflex-mediated adverse drug reactions (ADRs) receive far less attention than drug-induced QT prolongation, torsades de pointes, and ventricular arrhythmias[9].

This review gives a scientific synthesis of available evidence and a pharmacovigilance-oriented analysis of drug-induced baroreceptor dysfunction. This narrative

review follows the principles for scientific review standards used in biomedical literature[10].

Literature search strategy

A thorough search of the Cochrane Library, PubMed, Google Scholar, Embase, and Scopus, and WHO-UMC pharmacovigilance publications was conducted using a variety of keyword combinations including the following: baroreceptor, baroreflex sensitivity, autonomic dysfunction, drug-induced, pharmaco-vigilance, cardiovascular adverse drug reactions, orthostatic hypotension, reflex tachycardia, syncope, and signal detection[11].

Inclusion criteria

Peer-reviewed clinical trials, case reports, mechanistic studies, and observational studies, pharmacovigilance database analyses, e.g. FAERS, VigiBase and studies that describe drug baroreflex interactions[12].

Exclusion criteria

Non-pharmacological studies unrelated to drug effects and Exclusion Criteria: Articles that do not report on cardiovascular or autonomic outcomes[12,13].

Baroreflex physiology and pathophysiology

Structure and function of baroreceptors

The baroreceptors, which are mostly found in the carotid sinus and aortic arch, are mechanosensitive nerve endings implanted in the elastic walls of arteries.. Their firing frequency relates directly to arterial stretch and pressure. Activation has an inhibitory effect on sympathetic outflow and an excitatory effect on parasympathetic activity, which decreases heart rate and vascular resistance[14].

Baroreflex Sensitivity (BRS)

BRS reflects responsiveness of the baroreflex arc and conventionally is measured using: sequence method Valsalva manoeuvre transfer function analysis.

Reduced BRS is associated with increased cardio-vascular mortality, autonomic neuropathy, and susceptibility to drug-induced ADRs[14,15].

Drug classes associated with baroreceptor dysfunction end

1. Vasodilators

Hydralazine, nitrates, and dihydropyridine calcium channel blockers reduce arterial pressure and cause reflex sympathetic activation, leading to tachycardia due to reduced baroreceptor stretch[15].

2. Beta-Blockers

Non-selective beta blockers may block the sympathetic compensation and can result in bradycardia or hypotension[16].

3. Opioids

Agents related to morphine and fentanyl depress central autonomic pathways and impair baroreflex mediated heart rate regulation[17].

4. Antipsychotics and antidepressants

Agents with α1-adrenergic blockade (eg, quetiapine, risperidone, amitriptyline) cause orthostatic hypotension due to impaired compensatory mechanisms of the autonomic system[18].

5. Antiarrhythmic agents

Drugs such as amiodarone and sotalol affect autonomic tone and thus predispose to bradyarrhythmias[18].

6. Anesthetic agents

The volatile anesthetics and propofol reduce sympathetic tone and baroreflex responsiveness[19].

Pharmacovigilance assessment of baroreceptor related adverse drug reactions

Limitations in current reporting systems

FAERS, VigiBase and EudraVigilance do not include spontaneous reporting database-specific classification for baroreceptor dysfunction. ADRs are reported using higher-level generic terms such as: syncope, brady-cardia, tachycardia, orthostatic hypotension. This leads to significant misclassification[20].

Signal detection methods

Pharmacovigilance relies on investigations of statistical disproportionality: (Reporting Odds Ratio (ROR), EBGM: Empirical Bayes Geometric Mean, PRR: Proportional Reporting Ratio, and BCPNN: Bayesian Confidence Propagation Neural Network) These instruments are able to identify signals associated with cardiovascular responses, but they are not very good at distinguishing effects unique to baroreflex[21].

Real-world evidence and digital health tools

The appearance of wearable devices, digital blood pressure monitors, and continuous ECG monitoring offers new opportunities for the detection of subtle baroreflex abnormalities in real time[22].

Regulatory implications

Regulatory agencies rarely require baroreflex testing for drug approval. Very limited guidance has been published on autonomic evaluation of ADRs, and the majority of this relates to QT interval evaluations[23].

DISCUSSION

This review highlights a major under investigated area of cardiovascular safety, namely drug-induced dysfunction of the baroreceptor mechanism. Though clinically relevant, mechanisms remain poorly represented in the pharmacovigilance paradigm. The baroreflex is an important regulatory system for the maintenance of blood pressure and heart rate; even subtle perturbations may expose patients to clinically significant ADRs[24]. Current literature would indicate that impairment of the baroreflex may contribute to syncope, arrhythmias, orthostatic hypotension, and sudden cardiac events. It remains, however, fragmented[25]. Most studies focus on the hemodynamic consequences of a single agent and without systematic assessment of the baroreflex arc. Pharmacovigilance databases categorize ADRs based upon their clinical manifestations rather than physiological mechanisms and hence are difficult to interpret mechanistically[26].

Identified gaps in evidence

- There is no specific category related to the dysfunction of the baroreceptors in any major pharmacovigilance system[27].
- The clinical studies related to BRS as a safety parameter are limited.
- Incomplete understanding of the mechanistic basis whereby drugs modulate baroreflex signalling pathways[28].

- Underreporting and misclassification of autonomic ADRs[29].
- Lack of predictive models for baroreflex impairment[30].
- Poor data in high-risk populations, including the elderly and those with autonomic neuropathy[31].
- Polypharmacy interactions unstudied despite common autonomic burden[32].
- Digital and wearable technologies are vastly underutilized in the detection of real-time autonomic dysfunction[33].
- No long-term follow-up studying progression or reversability of drug-induced baroreflex impairment[33].

CONCLUSIONS

Drug-induced dysfunction of baroreceptors is an under-appreciated cause of cardiovascular ADRs and represents one of the major limitations of contemporary pharmacovigilance practice. Improved detection and understanding relies on the incorporation of baroreflex end-points into clinical trials, better ADR classification systems, and the implementation of high order digital and computational methodologies. Reinforcing pharm-acovigilance frameworks with the inclusion of baroreflex related safety monitoring has the potential to prevent major cardiovascular events and inform safer prescribing.

ACKNOWLEDGEMENTS

The author would like to acknowledge all researchers whose work contributed to the evidence summarized in this review.

AUTHOR'S CONTRIBUTIONS

Said SS: writing the original draft, methodology, investigation. **Simai B:** review, editing. **Mwadini AM:** methodology, review. **Rashid SS:** literature survey, data processing. Final manuscript was checked and approved by both authors.

DATA AVAILABILITY

Upon reasonable request, the corresponding author will provide the datasets created or examined during this investigation.

CONFLICT OF INTEREST

None to declare.

REFERENCES

1. Rienzo MD, Parati G, Radaelli A, Castiglioni P. Baroreflex contribution to blood pressure and heart rate oscillations: time scales, time-variant characteristics and nonlinearities. Philos Transact A Math Phys Eng Sci 2009;367(1892):1301. *https://doi.org/10.1098/rsta.2008.0274*
2. Klabunde RE. Cardiovascular Physiology Concepts. 3rd edition. Wolters Kluwer 2021.
3. Mahdi A, Sturdy J, Ottesen JT, *et al*. Modeling the afferent dynamics of the baroreflex control system. PLOS Comput Biol 9(12): e1003384. *https://doi.org/10.1371/journal.pcbi.1003384*
4. Rovere MTL, Pinna GD, Raczak G. Baroreflex sensitivity: Measurement and clinical implications. Annals Noninv Electrocardiol 2008; 13(2): 191-207. *https://doi.org/10.1111/j.1542-474X.2008.00219.x*
5. Mastuda T, Bates JN, Lewis SJ, *et al*. Modulation of baroreceptor activity by nitric oxide and S-nitrosocysteine | Circ Res 1995; 76(1): 426-433. *https://doi.org/10.1161/01.RES.76.3.426*
6. Baroreflex buffering and susceptibility to vasoactive drugs. Circulation 2002; 105(12): 1459-1464. *https://doi.org/10.1161/01.CIR.0000012126.56352.FD*
7. Baroreflex failure: Symptoms, causes, and treatment.. [cited 2025 Dec 8].
8. Gholami K, Ziaie S, Shalviri G. Adverse drug reactions induced by cardiovascular drugs in outpatients. Pharm Pract 2008 Mar 10;6(1):51. PMID:25170364 *https://doi.org/10.4321/S1886-36552008000100008*
9. Hsieh DY, Lai YR, Huang CC, *et al*. Baroreflex sensitivity as a surrogate biomarker for concurrently assessing the severity of arterial stiffness and cardiovascular autonomic neuropathy in individuals with type 2 diabetes. J Pers Med 2024 May 3;14(5):491. PMID:38793073 *https://doi.org/10.3390/jpm14050491*
10. Bhanu C, Nimmons D, Petersen I, *et al*. Drug-induced orthostatic hypotension: A systematic review and meta-analysis of randomised controlled trials. PLoS Med 2021; 18(11): e1003821. *https://doi.org/10.1371/journal.pmed.1003821*
11. Gerlach DA, Manuel J, Hoff A, *et al*. Novel approach to elucidate human baroreflex regulation at the brainstem level: Pharmacological testing during fMRI. Front Neurosci 2019 Mar 5; 13:193. PMID:30890917 *https://doi.org/10.3389/fnins.2019.00193*
12. AA Kroon, PW de Leeuw. Baroreflex activation in drug-resistant hypertension. Europ Cardiol 2008:4(2):56-8. *https://doi.org/10.15420/ecr.2008.4.2.56*
13. Lin YD, Diedrich A. Editorial: Methods on the assessment of human baroreflex function. Front Neurosci 2022 June 28;16:965406. PMID:35837120 *https://doi.org/10.3389/fnins.2022.965406*
14. A.F. Sved, E.M. Stricker, S.D. Stocker. Baroreceptor responses. Module Biomed Sci 2015;3: 440-442. *https://doi.org/10.1016/B978-0-12-801238-3.03960-X*
15. Palmero HA, Caeiro TF, Iosa DJ, Bas J, Baroreceptor reflex sensitivity index derived from phase 4 of the Valsalva manoeuvre. Hypertension 1981;3:II134–7. *https://doi.org/10.1161/01.HYP.3.6_Pt_2.II-134*
16. Lipman RD, Salisbury JK, Taylor JA. Spontaneous indices are inconsistent with arterial baroreflex gain. Hypertension 2003; 42: 481–487. *https://doi.org/10.1161/01.HYP.0000091370.83602.E6*
17. Ruyle BC, Masud S, Kesaraju R, *et al*. Peripheral opioid receptor antagonism alleviates fentanyl-induced cardiorespiratory depression and is devoid of aversive behaviour eLife 2024;13:RP104469. *https://doi.org/10.7554/eLife.104469.2*
18. Sica DA. Alpha1-adrenergic blockers: Current usage considerations. The J Clin Hypertension 2005; 702-767. *https://doi.org/10.1111/j.1524-6175.2005.05300.x*
19. Mackin C, DeWitt ES, Black KJ, *et al*. Intravenous amiodarone and sotalol impair contractility and cardiac output, but procainamide does not: A Langendorff study. J Cardiovasc Pharmacol Ther 2018 Nov 29; 24(3):288. *https://doi.org/10.1177/1074248418810811*
20. Rovere MTL, Maestri R, Pinna GD. Baroreflex sensitivity assessment - latest advances and strategies. Europ Cardiol 2011; 7(2):89–92. *https://doi.org/10.15420/ecr.2011.7.2.89*
21. Montastruc JL, Sommet A, Bagheri H, Lapeyre-Mestre M. Benefits and strengths of the disproportionality analysis for

identification of adverse drug reactions in a pharmacovigilance database. Br J Clin Pharmacol 2011 Dec;72(6):905. *https://doi.org/10.1111/j.1365-2125.2011.04037.x* PMID:21658092 PMCid:PMC3244636

22. Laudenzi BM, Cucino A, Lassola S, Balzani E, Müller LO. Predicting in-hospital indicators from wearable-derived signals for cardiovascular and respiratory disease monitoring: An in silico study. PLOS Digital Health 2025; 4(10): e0001041. *https://doi.org/10.1371/journal.pdig.0001041*
23. S7A Safety Pharmacology Studies for Human Pharmaceuticals.
24. Jordan J, Tank J, Shannon JR, *et al*. Baroreflex buffering and susceptibility to vasoactive drugs. Circulation 2002. 105(12): 1459-1464. *https://doi.org/10.1161/01.cir.0000012126.56352.fd*
25. Biaggioni I, Shibao CA, Diedrich A, *et al*. Blood pressure management in afferent baroreflex failure: JACC review topic of the week. J Am Coll Cardiol 2019; 10;74(23):2939-2947. PMID: 31806138 *https://doi.org/10.1016/j.jacc.2019.10.027*
26. Smith SA, Stallard TJ, Salih MM, Littler WA. Can sinoaortic baroreceptor heart rate reflex sensitivity be determined from phase IV of the Valsalva manoeuvre? Cardiovasc Res 1987;21:422–7. *https://doi.org/10.1093/cvr/21.6.422*
27. Watkins LL, Grossman P, Sherwood A, *et al*. Noninvasive assessment of baroreflex control in borderline hypertension. Hypertension 1996; 28(2):238-243 *https://doi.org/10.1161/01.HYP.28.2.238*
28. Pinna GD, Maestri R, New criteria for estimating baroreflex sensitivity using the transfer function method, Med Biol Eng Comput 2002;40:79–84. *https://doi.org/10.1007/BF02347699*
29. Hazzel L, Shakir SAW. Under-reporting of adverse drug reactions : A systematic review. Drug Saf 2006;29:5. *https://doi.org/10.2165/00002018-200629050-00003*
30. Parati G, Di Rienzo M, Bertinieri G, *et al*. Evaluation of the baroreceptor-heart rate reflex by 24-hour intra-arterial blood pressure monitoring in humans. Hypertension 1988;12:214–22. *https://doi.org/10.1161/01.HYP.12.2.214*
31. Klop M, Claassen JAHR, Mol A, *et al*. Age and orthostatic hypotension are associated with baroreflex sensitivity and cerebral oxygenation after postural change. Auton Neurosci 2025 Aug 1;260:103291. PMID:40440862 *https://doi.org/10.1016/j.autneu.2025.103291*
32. Samajdar SS, Das S, Sarkar S, *et al*. Association between polypharmacy and cardiovascular autonomic function among elderly patients in an urban municipality area of Kolkata, India: A record-based cross-sectional study. Geriatrics. 2022 Nov 29;7(6):136. PMID:36547272 *https://doi.org/10.3390/geriatrics7060136*
33. Fuchsa B, Ejtehadi M, Cisnal A, *et al*. Detection of autonomic dysreflexia in individuals with spinal cord injury using multimodal wearable sensors 2025. *https://doi.org/10.48550/arXiv.2508.03715*