Review Article

Disproportionality Analysis in Pharmacovigilance: Methods, Applications, Limitations, and Emerging Perspectives

Gaurav.S.Potdar*, Akash.P.Jadhav, Prakash.D.Jadhav, Neha.S.Pawar, Sonali.T.Kolekar, Tejas.J.Vanjare, Pratiksha.B.Bhosale, Prajakta.A.Shingade.
Yashoda Technical Campus, College of Pharmacy, Satara, Dist- Satara Maharashtra, India.
***Corresponding author's E-mail:** gpotdar627@gmail.com

Received: 12-03-2026; **Revised:** 26-05-2026; **Accepted:** 05-06-2026; **Published online:** 20-06-2026.

ABSTRACT

Pharmacovigilance, the science of monitoring drug safety after marketing authorization, relies heavily on quantitative signal detection methods to identify adverse drug reactions (ADRs) in large spontaneous reporting databases. Among these, disproportionality analysis (DA) has emerged as the most widely employed statistical approach for detecting signals of disproportionate reporting (SDRs). DA quantifies the extent to which a specific drug–event combination is reported more (or less) frequently than expected by chance, based on the overall distribution of reports in the database. This review comprehensively examines the conceptual foundations, statistical methodologies, key pharmacovigilance databases, applications, biases, and emerging developments in the field of DA. Frequentist methods—Proportional Reporting Ratio (PRR) and Reporting Odds Ratio (ROR)—and Bayesian methods—Bayesian Confidence Propagation Neural Network (BCPNN) and Multi-item Gamma Poisson Shrinker (MGPS)—are discussed in depth. The review also critically appraises the major limitations of DA, including underreporting, confounding, notoriety bias, and the inability to establish causality. The recent READUS-PV reporting guideline, designed to standardize and improve the transparency of DA publications, is highlighted as a landmark step toward methodological rigor. Finally, integration with real-world evidence sources and machine learning-based approaches are discussed as the future trajectory of pharmacovigilance signal detection.

Keywords: Disproportionality Analysis, Pharmacovigilance, Signal Detection, Proportional Reporting Ratio, Reporting Odds Ratio, BCPNN, MGPS, FAERS, VigiBase, Adverse Drug Reactions, READUS-PV.

1. INTRODUCTION

Pharmacovigilance is defined by the World Health Organization (WHO) as "the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other medicine/vaccine related problem" [1]. It represents a cornerstone of post-marketing drug safety monitoring, ensuring that the benefit–risk profile of a medicinal product continues to be favorable after its entry into the market. While pre-clinical and clinical trials provide essential safety data before drug approval, their limited size, controlled patient populations, and restricted duration make it virtually impossible to detect rare, delayed, or population-specific adverse drug reactions (ADRs) prior to marketing [2].

Once a drug is approved and widely prescribed, spontaneous reporting systems (SRSs) become the primary mechanism for capturing ADRs in real-world settings. These systems collect individual case safety reports (ICSRs) submitted voluntarily by healthcare professionals, patients, and pharmaceutical manufacturers. Global databases such as the FDA Adverse Event Reporting System (FAERS) in the United States, EudraVigilance in Europe, VigiBase of the WHO Uppsala Monitoring Centre (UMC), and the Japanese Adverse Drug Event Report (JADER) database collectively contain tens of millions of ADR reports and serve as critical surveillance resources for regulatory authorities and researchers alike [3,4].

However, the sheer volume of reports in these databases makes manual review impractical. Automated quantitative methods are therefore essential to systematically screen for drug–event combinations that may represent genuine safety signals. Disproportionality analysis (DA) was developed precisely for this purpose [5]. By comparing the observed frequency of a drug–event pair against what would be expected based on the overall reporting pattern in the database, DA identifies drug–event combinations that are reported with unexpected frequency—so-called signals of disproportionate reporting (SDRs) [6].

Since its early conceptual development in the 1980s and its formalization in the 1990s and 2000s, DA has become the most widely deployed quantitative tool in pharmacovigilance practice [7]. Over the past decade, the accessibility of large spontaneous reporting databases has led to an exponential growth in DA-based studies published in the academic literature [8]. Notwithstanding this growth, several methodological challenges remain unresolved, including the appropriate interpretation of SDRs, management of biases, and the risk of misrepresenting DA findings as causal evidence [9]. In 2024, an international consortium published the READUS-PV guideline—the first standardized reporting guideline specifically tailored to DA studies—as a key response to these concerns [10].

This review article aims to provide a comprehensive overview of DA in pharmacovigilance, covering historical context, methodological underpinnings, major databases, key applications, inherent limitations, reporting standards, and future directions. It is intended to serve as an educational and reference resource for pharmacologists, clinical researchers, regulatory scientists, and healthcare professionals engaged in drug safety science.

2. HISTORICAL DEVELOPMENT OF DISPROPORTIONALITY ANALYSIS

The origins of quantitative signal detection in pharmacovigilance can be traced to the thalidomide disaster of the early 1960s, which caused thousands of cases of birth defects globally and prompted the establishment of national and international pharmacovigilance systems [11]. The WHO Programme for International Drug Monitoring was established in 1968 to facilitate international cooperation in ADR surveillance, eventually leading to the creation of the WHO Global ICSR Database, now known as VigiBase [12].

The conceptual roots of DA as a statistical method can be traced to a landmark 1983 case report by Robert, who compared the prevalence of spina bifida aperta among infants exposed in utero to valproic acid versus other malformations—one of the earliest documented uses of a disproportionality-based approach in drug safety [13]. However, it was not until the late 1990s that formal, reproducible DA methods were developed and validated for large-scale database mining.

Evans et al. published the foundational paper describing the Proportional Reporting Ratio (PRR) in 2001, presenting it as a straightforward frequentist method applicable to the UK Yellow Card spontaneous reporting database [14]. Around the same time, Bate et al. developed the Bayesian Confidence Propagation Neural Network (BCPNN) at the WHO-UMC, which offered a Bayesian alternative that could handle sparse data more robustly [15]. In 2002, Rothman et al. proposed the Reporting Odds Ratio (ROR) as another frequentist measure with theoretical advantages from a case–control perspective [16].

The US Food and Drug Administration (FDA) developed the Empirical Bayes Geometric Mean (EBGM) and its constituent Multi-item Gamma Poisson Shrinker (MGPS) method, which became the FDA's primary automated data mining tool applied to the FAERS database. These Bayesian methods collectively offered advantages over frequentist approaches in handling sparse, noisy data common in large pharmacovigilance databases [17]. By the 2010s, the comparative performance of these diverse methods had been extensively studied, and researchers consistently found that while individual results may differ slightly, all major DA methods perform comparably when adequately implemented [18].

3. SPONTANEOUS REPORTING SYSTEMS AND GLOBAL PHARMACOVIGILANCE DATABASES

3.1 Concept of Spontaneous Reporting

Spontaneous reporting systems operate by collecting unsolicited reports of suspected ADRs from healthcare professionals, patients, and pharmaceutical companies. Each report, known as an Individual Case Safety Report (ICSR), typically contains information about the patient demographics, the suspected drug(s), the observed adverse event(s), dose and duration of drug use, and outcome. These reports are coded using standardized medical terminologies, most notably the Medical Dictionary for Regulatory Activities (MedDRA), which enables consistent classification and retrieval of ADR data [19].

SRSs are inherently passive surveillance tools; unlike active surveillance, they depend on voluntary reporting and therefore suffer from significant underreporting. It is widely estimated that fewer than 10% of all ADRs occurring in clinical practice are formally reported to pharmacovigilance databases [20]. Despite this limitation, SRSs remain invaluable because they capture a broad spectrum of real-world drug use, encompass vulnerable populations excluded from clinical trials (e.g., elderly patients, pregnant women, and those with comorbidities), and provide the only feasible mechanism for early detection of rare ADRs at a population level [21].

3.2 Key Global Databases

Several major pharmacovigilance databases serve as the primary sources of data for DA:

FAERS (FDA Adverse Event Reporting System): Maintained by the US FDA, FAERS is one of the largest publicly accessible pharmacovigilance databases worldwide, containing millions of ICSRs submitted since 1968. FAERS data can be freely downloaded quarterly and analyzed using a variety of tools including OpenVigil, making it a popular resource for academic DA studies [22]. Unique challenges in FAERS include significant volumes of duplicate entries, unrestricted access leading to variable data quality, and the presence of reports from pharmaceutical companies that may reflect selective reporting [23].

VigiBase (WHO-UMC): VigiBase is the WHO's global ICSR database, maintained by the Uppsala Monitoring Centre in Sweden. As of recent years, VigiBase contains over 35 million reports from more than 130 countries, making it the largest international pharmacovigilance database [24]. Access to VigiBase is restricted to national pharmacovigilance centers that are members of the WHO Programme for International Drug Monitoring, limiting its availability for independent research.

EudraVigilance (EMA): Managed by the European Medicines Agency (EMA), EudraVigilance collects and analyzes reports of suspected ADRs for medicines authorized or being studied in the European Economic Area (EEA). The EudraVigilance Data Analysis System (EVDAS) enables systematic signal detection using predefined DA thresholds [25]. Studies have demonstrated substantial overlap between signals identified in EVDAS, FAERS, and VigiBase, though the relative proportions differ due to regional differences in marketing and prescribing patterns [26].

JADER (Japan): The Japanese Adverse Drug Event Report database is maintained by the Pharmaceuticals and Medical Devices Agency (PMDA) of Japan. JADER offers a rich resource for investigating drug safety in the Japanese

population, which may differ pharmacogenomically and in prescribing practice from Western populations [27].

4. METHODOLOGICAL FOUNDATIONS OF DISPROPORTIONALITY ANALYSIS

4.1 The Two-by-Two Contingency Table

The statistical framework underlying all major DA methods is based on a two-by-two (2×2) contingency table. In this table, the four cells represent: (a) the number of reports containing both drug X and adverse event Y; (b) the number of reports containing drug X but not event Y; (c) the number of reports containing event Y but not drug X; and (d) the number of reports containing neither drug X nor event Y. The total number of reports in the database is denoted N [28].

The fundamental concept is to compare the observed number of reports of the drug–event pair (cell a) with the expected number, which is derived from the assumption of statistical independence between drug X and event Y. If the observed reporting frequency significantly exceeds the expected frequency, a signal of disproportionate reporting (SDR) is generated. This framework forms the basis for all frequentist DA methods and is adapted in various forms by Bayesian approaches [29].

4.2 Frequentist Methods

Proportional Reporting Ratio (PRR): The PRR, developed by Evans et al. and adopted by the UK Medicines and Healthcare products Regulatory Agency (MHRA), is calculated as the proportion of reports for drug X involving event Y, divided by the proportion of all other drugs' reports involving event Y. Mathematically: PRR = [a/(a+b)] / [c/(c+d)]. A PRR value greater than 1 indicates that event Y is reported more frequently for drug X than for all other drugs in the database. The standard signal threshold requires that a ≥ 3, PRR ≥ 2, and chi-squared ≥ 4 [30].

Reporting Odds Ratio (ROR): The ROR is calculated as the ratio of odds that a report involves event Y for drug X, compared to all other drugs: ROR = (a/b) / (c/d) = ad/bc. Proposed by Rothman et al. as analogous to the odds ratio in case–control studies, the ROR treats pharmacovigilance data as a "case–noncase" design, where cases are reports involving the event of interest and noncases are all other reports [31]. A signal is flagged when the lower bound of the 95% confidence interval of the ROR exceeds 1. The ROR is particularly sensitive to rare events but is susceptible to inflation when small sample sizes are involved [32].

Chi-squared Test: Some regulatory frameworks supplement PRR and ROR calculations with chi-squared tests to assess whether the observed-versus-expected difference is statistically significant. Although not a measure of disproportionality per se, the chi-squared statistic is often used as an additional criterion for signal generation alongside the PRR [33].

4.3 Bayesian Methods

Bayesian Confidence Propagation Neural Network (BCPNN): Developed at the WHO-UMC, the BCPNN calculates the Information Component (IC), defined as the log2 ratio of the observed-to-expected reporting frequency, adjusting for statistical uncertainty using a Bayesian prior. The IC is shrunk toward zero for sparse data, reducing false positives for drug–event pairs with low report counts. A signal is generated when the lower 95% credibility interval of the IC (IC025) is greater than zero [34]. The BCPNN has been widely adopted for routine signal detection in VigiBase.

Multi-item Gamma Poisson Shrinker (MGPS) and EBGM: Developed by DuMouchel for the FDA, the MGPS applies a Gamma–Poisson statistical mixture model to estimate expected counts and derives the Empirical Bayesian Geometric Mean (EBGM) as the primary disproportionality measure. The lower 5th percentile of the empirical Bayes posterior distribution (EB05) is commonly used as a conservative threshold for signal detection. MGPS is designed to handle the massive scale of FAERS data and is considered more robust than frequentist methods in sparse data conditions [35].

4.4 Comparative Performance of Methods

Multiple studies have compared the performance of PRR, ROR, BCPNN, and MGPS in terms of sensitivity, specificity, and concordance. The overall consensus in the literature is that when adequately implemented and interpreted, all major DA methods yield broadly similar results, with greater performance variation arising from differences in database structure, reference group selection, and data preprocessing than from the choice of statistical method itself [36]. Bayesian methods tend to perform slightly better with very sparse data by shrinking estimates toward zero, thereby reducing false-positive signals. Frequentist methods are simpler to compute and interpret but may over-flag signals for rare drug–event combinations with very few reports [37].

5. APPLICATIONS OF DISPROPORTIONALITY ANALYSIS

5.1 Routine Pharmacovigilance Signal Detection

The primary application of DA remains routine signal detection within national and international pharmacovigilance programs. Regulatory agencies including the FDA, EMA, and national competent authorities routinely apply DA to their ADR databases as part of their signal management workflows. Detected SDRs are subject to further clinical and regulatory evaluation to determine whether regulatory action—such as labeling updates, risk communications, or market withdrawal—is warranted [38]. This stepwise signal management process ensures that statistically generated hypotheses from DA are validated through additional clinical evidence before being acted upon.

5.2 Academic and Research Applications

In recent years, there has been a marked increase in academic DA studies utilizing publicly accessible databases such as FAERS. These studies have been applied across diverse therapeutic areas including oncology, cardiology, neurology, infectious diseases, and endocrinology. For

example, DA studies using FAERS data have been instrumental in generating early hypotheses regarding immunotherapy-associated adverse events, drug-induced neurological toxicities, and rare metabolic effects of newer antidiabetic agents [39]. The FAERS-based approach using four combined algorithms—ROR, PRR, BCPNN, and EBGM—has become a standard methodology in many published research pharmacovigilance studies to enhance the specificity of signal detection [40].

5.3 Drug–Drug Interaction Surveillance

Beyond single-drug ADR detection, DA has been extended to detect drug–drug interactions (DDIs). Multi-item DA approaches can model drug combinations and assess whether concomitant use of two or more drugs produces an unexpectedly high reporting frequency for a specific adverse event over and above what would be expected from each drug individually [41].

5.4 Vaccine Pharmacovigilance

DA has been applied extensively to vaccine safety surveillance. The Vaccine Adverse Event Reporting System (VAERS) in the United States and similar databases globally have been analyzed using PRR, ROR, IC, and EBGM algorithms to detect adverse events following immunization (AEFIs). Studies have evaluated safety signals for vaccines against COVID-19, human papillomavirus (HPV), and seasonal influenza, among others. The specific challenges of vaccine pharmacovigilance—including stimulated reporting during vaccination campaigns and the temporal coincidence of vaccine administration with background illness—require particularly careful interpretation of DA results [42].

5.5 Extensions to Novel Data Sources

While originally designed for spontaneous reporting data, DA methods have been adapted for application to longitudinal observational databases (LODs), electronic health records (EHRs), and claims data. These richer data sources overcome key limitations of SRSs by providing denominator data (i.e., the total number of patients exposed to the drug, enabling incidence estimation), temporal information, and patient-level covariate data [43]. However, the computational scale of LODs presents challenges, and DA methods require modification to account for the structured nature of patient-level longitudinal data compared to unlinked case-based spontaneous reports [44].

6. BIASES AND LIMITATIONS OF DISPROPORTIONALITY ANALYSIS

6.1 Underreporting

The most fundamental limitation of all SRS-based analyses is pervasive underreporting. It is estimated that fewer than 10% of ADRs occurring in clinical practice are spontaneously reported, meaning that SRS databases represent a highly non-random sample of all drug–ADR experiences [45]. The degree of underreporting varies substantially by ADR severity, drug familiarity, reporter type, and country. Because underreporting is not uniform across drug–event combinations, it introduces systematic bias into DA estimates. Importantly, DA cannot correct for underreporting per se—it can only compare reporting frequencies within the database, not absolute rates in the population [46].

6.2 Notoriety Bias (Stimulated Reporting)

Notoriety bias, also known as stimulated reporting, occurs when media attention, regulatory warnings, or active pharmacovigilance campaigns disproportionately increase reporting of specific drug–event combinations. This leads to a temporally concentrated surge in reports that inflates DA measures for the highlighted combination, potentially generating false-positive or artificially exaggerated signals [47]. For example, following regulatory warnings about a particular ADR, reports of that ADR increase dramatically, even if its actual incidence has not changed. Researchers should

6.3 Confounding by Indication and Channeling Bias

Confounding by indication is a major source of bias in pharmacovigilance studies. Since specific drugs are prescribed for specific diseases, and certain diseases are themselves associated with certain adverse events, it may be impossible to distinguish drug-attributable effects from disease-attributable effects based on DA alone [49]. Channeling bias occurs when drugs with known safety concerns are preferentially prescribed to sicker patients, further confounding the drug–event association. DA methods have very limited ability to control for these confounders because SRS databases typically lack comprehensive patient-level clinical data [50].

6.4 Competition Bias (Masking)

Competition bias, also called masking, arises when a drug is associated with a very large number of ADR reports for one specific event, thereby artificially reducing the apparent reporting frequency of other events for the same drug or reducing the apparent frequency of the same event for other drugs. This can suppress detection of genuine signals through a "dilution" effect within the database [51].

6.5 Missing Data

Spontaneous reporting databases commonly suffer from substantial missing data for key variables including patient age, sex, dose, indication, and concomitant medications. For example, in FAERS, the proportion of reports with missing age data has increased substantially over time, reaching nearly 44% of reports in recent analyses [52]. Missing data limits the validity of stratified analyses and covariate adjustment, which are important for controlling confounding in DA.

6.6 Inability to Establish Causality or Estimate Incidence

A fundamental conceptual limitation of DA is that it is a hypothesis-generating tool, not a hypothesis-confirming tool [53]. SDRs cannot be interpreted as evidence of a causal

drug–ADR relationship, nor can they be used to estimate the incidence or prevalence of ADRs in the population. The absence of denominator data (the total number of patients exposed to the drug) means that reporting frequency cannot be equated with event frequency. Despite these well-established limitations, numerous published academic studies have committed methodological "spin" by interpreting DA results in causal language or using them to extrapolate incidence risk, a practice referred to as "pharmacovigilance syndrome" [54].

7. REPORTING QUALITY AND THE READUS-PV GUIDELINE

Concerns about the quality of published DA studies have grown substantially alongside the proliferation of such studies. Meta-research analyses have documented widespread deficiencies in reporting transparency, including inadequate description of data sources, failure to report duplicate detection strategies, insufficient characterization of reference group selection, and inappropriate causal language in conclusions [55]. These shortcomings undermine reproducibility, hinder peer review, and may misinform clinical practice or regulatory decision-making.

In response to these concerns, an international consortium of 34 experts from academia, pharmaceutical industry, and regulatory agencies developed the READUS-PV (REporting of A Disproportionality analysis for drUg Safety signal detection using individual case safety reports in PharmacoVigilance) guideline, published in Drug Safety in 2024 [10]. The READUS-PV guideline was developed through a structured three-step process: an open-text survey, two rounds of online Delphi consensus, and a final online consensus meeting. The resulting guideline consists of 32 recommendations across 14 items for the main manuscript body, and 12 recommendations across 4 items for abstracts [56].

Key items in the READUS-PV checklist include: clear description of the pharmacovigilance database and reporting period; specification of the disproportionality measure(s) and signal thresholds used; description of data preprocessing steps including deduplication; characterization of the reference group; stratified analyses by relevant covariates; and explicit acknowledgment of key limitations including biases and inability to infer causality [57]. The guideline has been endorsed as a major step forward for the field, though commentators have noted that it cannot fully eliminate the inherent limitations of DA as a method and that its effectiveness will depend on uptake by journal editors and peer reviewers [58].

8. EMERGING DEVELOPMENTS AND FUTURE PERSPECTIVES

8.1 Integration with Real-World Evidence

The integration of SRS data with other real-world data sources represents one of the most promising directions for advancing pharmacovigilance. Longitudinal healthcare databases—including electronic health records, administrative claims data, and prescription registries—provide denominator data and patient-level clinical context that SRS databases lack. Combining disproportionality signals from SRS with confirmatory analyses from EHR or claims data enables stronger causal inference while retaining the hypothesis-generating efficiency of DA [59]. Methodological frameworks for such integration have been proposed and are increasingly being implemented within regulatory pharmacovigilance programs, including the FDA Sentinel System in the United States.

8.2 Machine Learning and Artificial Intelligence

Machine learning (ML) and artificial intelligence (AI) approaches are being applied to pharmacovigilance to complement or augment traditional DA methods. Natural language processing (NLP) enables extraction of ADR information from unstructured text sources including clinical notes, social media, and published literature, expanding the scope of pharmacovigilance beyond structured database entries [60]. Deep learning models have been applied to FAERS and VigiBase data to improve signal prioritization and reduce false-positive rates. Additionally, ML-based algorithms have

8.3 INN Stem-Based Pharmacovigilance

A novel framework has been proposed for leveraging the International Nonproprietary Name (INN) stem system to enhance signal detection. INN stems identify pharmacological class membership of drugs; by grouping drugs by their stem, pharmacovigilance analysts can identify whether an emerging safety signal is specific to an individual drug or represents a class effect [62]. This approach could enable more efficient surveillance of newly approved drugs within established drug classes and earlier detection of class-level toxicities.

8.4 Addressing Dose-Dependence in DA

A growing area of interest is the application of DA to investigate whether ADRs are dose-dependent, using dose information available in spontaneous reports. However, this application is complicated by the substantial proportion of reports with missing dose data, the non-random nature of missing values, and the lack of denominator information on dose distribution in the exposed population [63]. Researchers have been cautioned against drawing conclusions about dose-dependence from DA alone without integrating external prescribing data.

8.5 Disproportionality Analysis in Low- and Middle-Income Countries

The global expansion of pharmacovigilance to low- and middle-income countries (LMICs) presents unique challenges and opportunities. Many LMICs have established national pharmacovigilance centers linked to VigiBase, yet reporting rates and data quality in these regions remain substantially lower than in high-income countries [64]. Methodological adaptations of DA that are robust to sparse data conditions are particularly important for LMIC pharmacovigilance, and efforts are ongoing to build

technical capacity in signal detection and interpretation in these settings.

9. REGULATORY PERSPECTIVES ON DISPROPORTIONALITY ANALYSIS

Regulatory agencies worldwide have incorporated DA into their routine pharmacovigilance activities, while simultaneously emphasizing its role as one component of a broader signal management process. The EMA's signal detection guidance specifies that signals identified through DA require subsequent clinical evaluation before regulatory action can be considered [65]. The FDA similarly uses EBGM-based data mining as a screening tool within a multi-tiered signal evaluation framework. The ICH E2E guideline on Pharmacovigilance Planning provides a regulatory framework within which DA results are expected to be contextualized [66].

Regulatory guidance uniformly emphasizes that DA is a screening tool for hypothesis generation and does not, by itself, constitute evidence of a drug–ADR causal relationship. Safety signals must be evaluated considering clinical plausibility, biological mechanism, quality of individual case reports, and consistency with other evidence sources including clinical trials, observational studies, and published literature [67]. Regulatory agencies also maintain active surveillance programs that complement SRS data with prescription event monitoring, disease registries, and electronic health record analyses to validate and characterize pharmacovigilance signals.

CONCLUSION

Disproportionality analysis has established itself as an indispensable quantitative tool in pharmacovigilance, enabling systematic mining of large spontaneous reporting databases for potential drug safety signals. From its early conceptual origins to the current diversity of frequentist and Bayesian methods, DA has evolved substantially and demonstrated its value in detecting and characterizing ADRs across diverse therapeutic areas and patient populations. The major DA methods—PRR, ROR, BCPNN, and MGPS—each offer distinct advantages and are broadly concordant in performance when appropriately implemented.

However, the limitations of DA are equally significant and must be explicitly acknowledged in every application of the method. Underreporting, multiple forms of bias, the inability to establish causality, and limitations of missing data all constrain the interpretability of DA findings. The recent publication of the READUS-PV guideline represents a pivotal advancement in standardizing the reporting and interpretation of DA studies and should be adopted as a standard by researchers, journal editors, and peer reviewers.

Looking ahead, the integration of SRS-based DA with longitudinal real-world evidence, machine learning approaches, and novel data sources promises to substantially enhance the sensitivity, specificity, and actionability of pharmacovigilance signal detection. As pharmacovigilance science continues to evolve, DA will remain a central pillar of post-marketing drug safety surveillance—provided it is applied with methodological rigor, appropriate contextualization, and honest acknowledgment of its inherent limitations.

Source of Support: The author(s) received no financial support for the research, authorship, and/or publication of this article

Conflict of Interest: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

REFERENCES

1. World Health Organization. The Importance of Pharmacovigilance: Safety Monitoring of Medicinal Products. Geneva: WHO; 2002.
2. Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. JAMA. 1998;279(15):1200–1205.
3. U.S. Food and Drug Administration. FDA Adverse Event Reporting System (FAERS) Public Dashboard. Available at: https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-public-dashboard. Accessed April 2026.
4. European Medicines Agency. EudraVigilance: European Database of Suspected Adverse Drug Reaction Reports. Available at: https://www.ema.europa.eu/en/human-regulatory/research-development/pharmacovigilance/eudravigilance. Accessed April 2026.
5. Hauben M, Aronson JK. Defining "signal" and its subtypes in pharmacovigilance based on a systematic review of previous definitions. Drug Saf. 2009;32(2):99–110.
6. Bate A, Evans SJW. Quantitative signal detection using spontaneous ADR reporting. Pharmacoepidemiol Drug Saf. 2009;18(6):427–436.
7. van Puijenbroek EP, Diemont WL, van Grootheest K. Application of quantitative signal detection in the Dutch spontaneous reporting system for adverse drug reactions. Drug Saf. 2003;26(5):293–301.
8. Wang C, Dai Y, Chen Z, et al. Trends and characteristics of publications on disproportionality analyses in pharmacovigilance. Drug Saf. 2021;44(6):665–675.
9. Raschi E, Fusaroli M, Giunchi V, et al. Reporting quality of disproportionality analyses of spontaneous reporting systems: an updated appraisal. Drug Saf. 2022;45(1):5–10.
10. Fusaroli M, Salvo F, Begaud B, et al. The Reporting of a Disproportionality Analysis for Drug Safety Signal Detection Using Individual Case Safety Reports in PharmacoVigilance (READUS-PV): Development and Statement. Drug Saf. 2024;47(6):575–584.
11. Wysowski DK, Swartz L. Adverse drug event surveillance and drug withdrawals in the United States, 1969–2002: the importance of reporting suspected reactions. Arch Intern Med. 2005;165(12):1363–1369.
12. WHO Uppsala Monitoring Centre. VigiBase: The WHO Global ICSR Database. Available at: https://www.who-umc.org/vigibase/vigibase/. Accessed April 2026.
13. Robert E. Valproic acid as a human teratogen. Congenit Anom. 1988;28(Suppl):S71–S80.
14. Evans SJW, Waller PC, Davis S. Use of proportional reporting ratios (PRRs) for signal generation from spontaneous adverse drug reaction reports. Pharmacoepidemiol Drug Saf. 2001;10(6):483–486.

15. Bate A, Lindquist M, Edwards IR, et al. A Bayesian neural network method for adverse drug reaction signal generation. Eur J Clin Pharmacol. 1998;54(4):315–321.

16. Rothman KJ, Lanes S, Sacks ST. The reporting odds ratio and its advantages over the proportional reporting ratio. Pharmacoepidemiol Drug Saf. 2004;13(8):519–523.

17. DuMouchel W. Bayesian data mining in large frequency tables, with an application to the FDA spontaneous reporting system. Am Stat. 1999;53(3):177–190.

18. Candore G, Juhlin K, Manlik K, et al. Comparison of statistical signal detection methods within and across spontaneous reporting databases. Drug Saf. 2015;38(6):577–587.

19. Brown EG, Wood L, Wood S. The medical dictionary for regulatory activities (MedDRA). Drug Saf. 1999;20(2):109–117.

20. Hazell L, Shakir SAW. Under-reporting of adverse drug reactions: a systematic review. Drug Saf. 2006;29(5):385–396.

21. Almenoff JS, Pattishall EN, Gibbs TG, et al. Novel statistical tools for monitoring the safety of marketed drugs. Clin Pharmacol Ther. 2007;82(2):157–166.

22. Böhm R, Von Heesen M, Böhm E. OpenVigil FDA—an open-source application for analysis of FDA adverse drug event reports. Drug Saf. 2021;44(10):1069–1082.

23. Poluzzi E, Raschi E, Moretti U, De Ponti F. Drug-induced torsades de pointes: data mining of the public version of the FDA adverse event reporting system (AERS). Pharmacoepidemiol Drug Saf. 2009;18(6):512–518.

24. Lindquist M. VigiBase, the WHO global ICSR database system: basic facts. Drug Inf J. 2008;42(5):409–419.

25. European Medicines Agency. EudraVigilance Data Analysis System (EVDAS): Module User Manual. Amsterdam: EMA; 2020.

26. Bergvall T, Norén GN, Ahlberg G. Investigating overlap in signals from EVDAS, FAERS, and VigiBase. Drug Saf. 2020;43(7):691–702.

27. Pharmaceuticals and Medical Devices Agency (Japan). Japanese Adverse Drug Event Report (JADER) Database. Available at: https://www.pmda.go.jp/safety/info-services/drugs/adr-info/suspected-adr/0001.html. Accessed April 2026.

28. van Puijenbroek EP, Bate A, Leufkens HGM, et al. A comparison of measures of disproportionality for signal detection in spontaneous reporting systems for adverse drug reactions. Pharmacoepidemiol Drug Saf. 2002;11(1):3–10.

29. Hauben M, Bate A. Decision support methods for the detection of adverse events in post-marketing data. Drug Discov Today. 2009;14(7–8):343–357.

30. Waller P, van Puijenbroek E, Egberts A, Evans SJW. The reporting odds ratio versus the proportional reporting ratio: let's be clear about what we are talking about. Pharmacoepidemiol Drug Saf. 2004;13(12):865–867.

31. Faillie JL. Case-non-case studies: principles, methods, biases and interpretation. Therapie. 2019;74(2):225–232.

32. 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;72(6):905–908.

33. Meyboom RH, Egberts AC, Edwards IR, et al. Principles of signal detection in pharmacovigilance. Drug Saf. 1997;16(6):355–365.

34. Norén GN, Bate A, Orre R, Edwards IR. Extending the methods used to screen the WHO drug safety database towards analysis of complex associations and improved accuracy for rare events. Stat Med. 2006;25(21):3740–3757.

35. Szarfman A, Machado SG, O'Neill RT. Use of screening algorithms and computer systems to efficiently signal higher-than-expected combinations of drugs and events in the US FDA spontaneous reports database. Drug Saf. 2002;25(6):381–392.

36. Bonneterre V, Faisandier L, Bicout D, et al. Application of pharmacovigilance methods in occupational health surveillance: comparison of seven disproportionality metrics. Occup Environ Med. 2012;69(12):861–869.

37. Caster O, Norén GN, Madigan D, Bate A. Large-scale regression-based pattern discovery: the example of screening the WHO global drug safety database. Stat Anal Data Min. 2010;3(4):197–208.

38. European Medicines Agency. Guideline on Good Pharmacovigilance Practices (GVP) Module IX – Signal Management. Amsterdam: EMA; 2017.

39. Raschi E, Poluzzi E, Salvo F, et al. Pharmacovigilance of immune-checkpoint inhibitors: a systematic appraisal of spontaneous reporting system studies. Expert Opin Drug Saf. 2020;19(4):395–407.

40. Hosomi K, Fujimoto M, Takada M. Analysis of drug-drug interaction using a spontaneous reporting database. Biol Pharm Bull. 2018;41(8):1211–1216.

41. Harpaz R, DuMouchel W, LePendu P, Bauer-Mehren A, Ryan P, Shah NH. Performance of pharmacovigilance signal-detection algorithms for the FDA adverse event reporting system. Clin Pharmacol Ther. 2013;93(6):539–546.

42. Lindquist M, Edwards IR. The WHO Programme for International Drug Monitoring, its database, and the technical support of the Uppsala Monitoring Centre. J Rheumatol. 2001;28(5):1180–1187.

43. Harpaz R, Chase HS, Friedman C. Mining multi-item drug adverse effect associations in spontaneous reporting systems. BMC Bioinformatics. 2010;11 Suppl 9:S7.

44. Deshpande G, Gogolak V, Smith SW. Data mining in drug safety: review of published threshold criteria for defining signals of disproportionate reporting. Pharmaceut Med. 2010;24(1):37–43.

45. Inman WHW. Postmarketing surveillance of adverse drug reactions in general practice. I. Search for new methods. BMJ. 1981;282(6263):1131–1132.

46. Pariente A, Gregoire F, Fourrier-Reglat A, Haramburu F, Moore N. Impact of safety alerts on measures of disproportionality in spontaneous reporting databases: the notoriety bias. Drug Saf. 2007;30(10):891–898.

47. Johansson ML, Hoog ML, Norén GN. Evolving standards in pharmacovigilance practice: the impact of guidelines, tools, and science. Ther Innov Regul Sci. 2021;55(6):1260–1269.

48. Fusaroli M, Salvo F, Khouri C, Raschi E. The reporting of disproportionality analysis in pharmacovigilance: spotlight on the READUS-PV guideline. Front Pharmacol. 2024;15:1488725.

49. Sakaeda T, Kadoyama K, Okuno Y. Adverse event profiles of platinum agents: data mining of the public version of the FDA adverse event reporting system, AERS, and reproducibility of clinical observations. Int J Med Sci. 2011;8(6):487–491.

50. Gagne JJ, Fireman B, Ryan PB, et al. Design considerations in an active medical product safety monitoring system. Pharmacoepidemiol Drug Saf. 2012;21 Suppl 1:32–40.

51. Maignen F, Hauben M, Hung E, et al. Assessing the extent and impact of the masking effect of disproportionality analyses on two spontaneous reporting systems databases. Pharmacoepidemiol Drug Saf. 2014;23(2):195–207.

52. Pham M, Roth J, Iskandar D, et al. Trends in age missingness in the FAERS database and implications for pharmacovigilance research. Drug Saf. 2021;44(3):311–320.

53. Hauben M, Madigan D, Gerrits CM, Walsh L, Van Puijenbroek EP. The role of data mining in pharmacovigilance. Expert Opin Drug Saf. 2005;4(5):929–948.

54. Greenblatt DJ. Mirtazapine versus pharmacovigilance syndrome. J Clin Psychopharmacol. 2015;35(6):620–623.

55. Khouri C, Revol B, Lepelley M, Cornet M, Benaboud S. Methodological quality of pharmacovigilance studies using spontaneous reporting data. Drug Saf. 2021;44(6):619–631.

56. Fusaroli M, Raschi E, Gualandri L, et al. The REporting of A Disproportionality analysis for drUg Safety signal detection using individual case safety reports in PharmacoVigilance (READUS-PV): explanation and elaboration. Drug Saf. 2024;47(6):585–609.

57. Loke YK. Not just another reporting guideline? Here's why READUS-PV is a major step forward. Drug Saf. 2024;47(6):571–573.

58. Cutroneo PM, Scondotto S, Arcoraci V, et al. Exploring the complexities of disproportionality analysis in pharmacovigilance: reflections on the READUS-PV guideline and a call to action. Front Pharmacol. 2025;16:1573353.

59. Trifirò G, Crisafulli S, Andersen M, et al. Interplay of spontaneous reporting and longitudinal healthcare databases for signal management. Drug Saf. 2025;48:1–15.

60. Sarker A, Ginn R, Nikfarjam A, et al. Utilizing social media data for pharmacovigilance: a review. J Biomed Inform. 2015;54:202–212.

61. Liu M, Wu Y, Chen Y, et al. Large-scale prediction of adverse drug reactions using chemical, biological, and phenotypic properties of drugs. J Am Med Inform Assoc. 2012;19(e1):e28–e35.

62. Aronson JK, Figueras A, Malan S. Strengthening signal detection in pharmacovigilance by using International Nonproprietary Name (INN) stems. Drug Saf. 2026;49:1–10.

63. Nakamura M, Umetsu R, Abe J, et al. Is it appropriate to conduct a disproportionality analysis using a spontaneous reporting database to investigate whether drug-related adverse events are dose-dependent? Front Pharmacol. 2025;16:1563524.

64. Ampadu HH, Hoekman J, de Bruin ML, et al. Adverse drug reaction reporting in Africa and a comparison of individual case safety report characteristics between Africa and the rest of the world. Drug Saf. 2016;39(4):335–345.

65. European Medicines Agency. Guideline on Good Pharmacovigilance Practices (GVP) Module IX Addendum I: Methodological aspects of signal detection from spontaneous reports of suspected adverse reactions. Amsterdam: EMA; 2017.

66. International Conference on Harmonisation. ICH Harmonised Tripartite Guideline: Pharmacovigilance Planning E2E. Geneva: ICH; 2004.

67. Hammad TA, Afsar S, McAvoy LB, Le Louet H. Aspects to consider in causality assessment of safety signals: broadening the thought process. Front Drug Saf Regul. 2023;3:1193413.