Integrative Pharmacovigilance: Monitoring Adverse Events of Herbal, Nutraceutical and Conventional Therapies

Priyanka T. Farakute[1], Sakshi B. Gaikwad, Nishant R. Koli, Pushpalata P. Sherekar[2]

Ashokrao Mane College of Pharmacy, Peth Vadgaon

Corresponding author: Priyanka T. Farakute[1]
Email: priyankaalekari92@gmail.com
Doi: **10.5281/zenodo.17101285**
Received: 25 June 2025
Accepted: 05 July2025

Abstract:

Integrative pharmacovigilance represents a vital methodology for monitoring adverse events (AEs) linked to both herbal nutraceuticals and conventional therapies. Given the increasing utilization of complementary and alternative medicines (CAMs), it is crucial to ensure the safety of these products. By employing integrated pharmacovigilance strategies for both herbal nutraceuticals and conventional therapies, AEs can be comprehensively captured, data analysed to identify potential safety signals and trends, and associated risks assessed. This methodology empowers healthcare professionals and regulatory agencies to make informed decisions, thereby enhancing patient safety and outcomes.

Integrative pharmacovigilance promotes a holistic understanding of the intricate interactions between herbal nutraceuticals and conventional therapies, facilitating more effective risk management and mitigation. The adoption of this approach allows for improved monitoring and management of AEs, alleviating the burden on healthcare systems and benefiting public health. Successful integrative pharmacovigilance necessitates collaboration among various stakeholders, including regulatory agencies, healthcare professionals, and industry partners.

By fostering cooperation, the safe use of herbal nutraceuticals and conventional therapies can be assured, thereby enhancing the overall effectiveness of the healthcare system. The integration of pharmacovigilance strategies for these two categories of therapies is essential for safeguarding public health and supporting evidence-based decision-making. By emphasizing integrative pharmacovigilance, the benefits of these products can be optimized while minimizing associated risks, thus ensuring both safety and efficacy. Ultimately, this approach will contribute to a more secure and effective healthcare environment, where patients can confidently utilize herbal nutraceuticals and conventional therapies under the guidance of knowledgeable healthcare professionals.

Keywords: Adverse Events Monitoring, Herbal Therapies, Integrative Pharmacovigilance, Public health, Patient safety.

Introduction:

Pharmacovigilance is defined as the study of the safety of marketed drugs within real-world clinical settings, aiming to identify previously unrecognized adverse events and enhance safety monitoring. Originally designed for pharmaceutical drugs, pharmacovigilance techniques have now been extended to evaluate the safety of various treatments, including herbal remedies, blood products, vaccines, and medical devices.[1]

The increasing utilization of herbal medications has led to a rise in reports of suspected toxicity and adverse events. Pharmacovigilance is essential for detecting adverse reactions, especially since many herbal products available in the market have not undergone comprehensive toxicity and pharmacology assessments.[2]

Quality concerns regarding herbal products, such as the use of substandard herbal materials, misidentification, inadequate processing, and contamination, can lead to unforeseen toxicity. Implementing Good Manufacturing Practice (GMP) standards may help mitigate some of these quality issues. Nonetheless, the global nature of the herbal medicine industry, characterized by inconsistent production standards and regulatory enforcement, suggests that low-quality products will likely continue to pose a challenge. [3,4,5]

Regulatory authorities are increasingly focused on the safety of herbal medicines, given the reported severe adverse effects, including hepatotoxicity, renal failure, and allergic reactions. In response to these concerns, the World Health Organization has established guidelines to address the growing significance of herbal medicine use globally. These guidelines aim to promote the safe application of herbal medicines and enhance pharmacovigilance practices.[6]

The rising popularity of herbal nutraceuticals alongside conventional therapies has created a critical need for integrative pharmacovigilance monitoring of adverse events associated with these products. As pharmacovigilance has traditionally concentrated on conventional pharmaceuticals, the increasing use of herbal nutraceuticals necessitates an expansion of pharmacovigilance initiatives to include these products. Considering the potential of herbal nutraceuticals to induce adverse reactions, interact with conventional medications, and affect public health, monitoring their safety profile is essential. Integrative pharmacovigilance provides a comprehensive approach by combining adverse event monitoring for both herbal nutraceuticals and conventional therapies. This methodology utilizes data from various sources, including spontaneous reporting systems and active surveillance, while promoting collaboration among stakeholders.[7]

Adverse effects of Herbal therapies:

Herbal therapies may result in a range of adverse effects, varying from mild to severe. Common issues include:
Gastrointestinal problems: Symptoms may include nausea, vomiting, abdominal pain, diarrhea, and loss of appetite.
Neurological effects: Potential effects include headaches, dizziness, confusion, hallucinations, seizures, and loss of consciousness.
Cardiovascular concerns: Issues may involve irregular heart rhythms, increased heart rate, and fluctuations in blood pressure.
Respiratory issues: Symptoms may consist of difficulty breathing, chest tightness, and wheezing.
Liver damage: Certain herbs, such as germander, comfrey, and kava, have been linked to liver toxicity.
Kidney damage: Herbs containing aristolochic acids, such as Aristolochia fangchi, are associated with kidney damage and an increased risk of urothelial cancer.
The consumption of specific herbs, including germander (Teucrium chamaedrys), comfrey (Symphytum spp.), and chaparral (Larrea tridentata), has been correlated with hepatotoxicity, often attributed to the presence of pyrrolizidine alkaloids. Additionally, noni juice (Morinda citrifolia), known locally as 'mengkudu,' has been reported to contain elevated potassium levels. Caution is advised for patients with renal issues, as high potassium levels can lead to arrhythmias and potentially myocardial infarction. [8,9]

Adverse Effects of Nutraceuticals:

Nutraceuticals, while generally regarded as safe, may lead to adverse effects, particularly when consumed in excessive amounts or in conjunction with other substances. Potential adverse effects may include:
Gastrointestinal Issues: Symptoms such as nausea, vomiting, diarrhea, constipation, abdominal pain, and cramping.
Allergic Reactions: Manifestations may include hives, skin rashes, itching, swelling, and in rare cases, anaphylaxis.

Interactions with Medications:

Blood Thinners: Certain nutraceuticals, such as omega-3 fatty acids and vitamin E, may heighten the risk of bleeding.

Blood Pressure Medications: Some nutraceuticals, including potassium supplements, can interact adversely with these medications.
Antidepressants: Nutraceuticals like St. John's Wort may interact with various antidepressant medications.

Other Potential Effects:
Liver Damage: High doses of certain nutraceuticals, such as vitamin A, may result in liver damage.
Kidney Stones: Elevated doses of vitamin C may increase the risk of developing kidney stones. [10,11,12]

Adverse Effects of Conventional Therapies:
Conventional therapies, which encompass pharmaceuticals and medical treatments, can also present various adverse effects. Common issues include:

Medication-Related Adverse Effects:
1. Allergic Reactions: Symptoms may include rashes, hives, itching, swelling, and anaphylaxis.
2. Gastrointestinal Problems: Potential issues include nausea, vomiting, diarrhea, constipation, and stomach pain.
3. Cardiovascular Effects: Possible changes in blood pressure, heart rate, and an increased risk of cardiovascular events.
4. Neurological Effects: Symptoms may consist of dizziness, headaches, confusion, and seizures.

Treatment-Related Adverse Effects:
1. Surgical Complications: Risks may include infection, bleeding, and scarring.
2. Chemotherapy Side Effects: Common side effects include hair loss, nausea, fatigue, and a heightened risk of infection.
3. Radiation Therapy Side Effects: Potential effects include fatigue, skin changes, and an increased risk of secondary cancers.
Long-Term Adverse Effects:
1.Dependence and Addiction: Certain medications may lead to physical dependence or addiction.
2. Organ Damage: Some medications can result in liver or kidney damage over time.
3. Increased Risk of Chronic Diseases: Certain treatments may elevate the risk of developing chronic conditions, such as diabetes or osteoporosis. [13,14]

Challenges in Pharmacovigilance of Herbal, Nutraceutical, Conventional therapies:
Herbal medications are intricate and chemically diverse products, in contrast to synthetic medicines, which generally consist of isolated single compounds. The chemical profile of herbal medications may be influenced by several factors, including:
Geographic origin: Climate, soil, and photoperiod can affect the chemical composition of herbs.
Genotype: The genetic characteristics of the plant can alter its chemical profile.
Plant parts: Various parts of the plant, such as leaves, stems, and roots, may exhibit distinct chemical properties.
Harvesting conditions: The season, time of year, and time of day can impact the chemical composition of herbs.
Preservation and processing: Methods of preservation and processing can influence the chemical profile of herbs.
Herb combinations: The interaction of different herbs or the processing of mixed herbs can lead to complex chemical interactions. [15]
Due to the inherent variability of herbal products, standardization concerning active components is often inadequate, resulting in products that may not be bioequivalent, even if they contain the same herbal ingredient. When aggregating accounts of adverse effects or efficacy, it is crucial to meticulously assess the differences and similarities in the findings. One potential strategy for identifying safety signals involves investigating groupings of herbs with similar compounds, based on their chemical or biological activity. This method can assist in identifying potential safety concerns and guiding further research. By comprehending the complexities of herbal medications, a more informed evaluation of their safety and efficacy can be achieved.[16]

The safety and toxicity of nutraceuticals—bioactive compounds or food-based products that offer health advantages beyond basic nutrition—have emerged as a critical area of research within nutrition and health disciplines. Nutraceuticals encompass a broad spectrum of products, including vitamins, minerals, botanical extracts, nutritional supplements, and functional foods. Nevertheless, the diverse formulations and varying quality of these products can create challenges for consumers in determining optimal dosages and ensuring safety.

While nutraceuticals are generally deemed safe when used as directed, excessive consumption may result in toxicity. The complexity of regulatory concerns within the nutraceutical industry arises from the extensive range of products, their potential health benefits, and the necessity to guarantee consumer safety. Regulatory issues may differ across countries and evolve with the emergence of new scientific evidence, underscoring the importance of remaining informed about regulatory frameworks and safety concerns. By understanding the potential risks and benefits associated with nutraceuticals, manufacturers, distributors, and consumers can collaborate to ensure the safe and effective utilization of these products.[17]

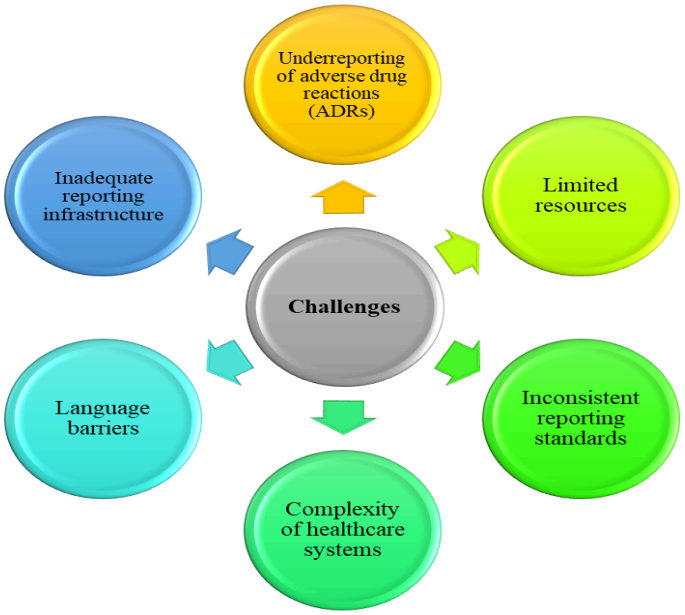

Fig. 1. Challenges in Pharmacovigilance

1. The underreporting of adverse drug reactions (ADRs) presents a significant challenge, as many ADRs remain unreported, complicating the accurate assessment of medication safety profiles.[18]
2. Limited resources, including inadequate funding and personnel, can hinder the effectiveness of pharmacovigilance initiatives.[19]
3. Variability in reporting standards across different regions and countries may result in inconsistencies in data collection and analysis.[20]
4. The complexity of healthcare systems can pose challenges in tracking and reporting ADRs effectively.[21]
5. Language barriers may impede the reporting and sharing of information regarding ADRs.[21]
6. Low and middle-income countries (LMICs) frequently lack adequate reporting infrastructure, which exacerbates the challenges associated with pharmacovigilance.[20]

These challenges underscore the necessity for enhanced pharmacovigilance systems, greater awareness, and improved collaboration to ensure the safe utilization of herbal, nutraceutical, and conventional therapies.

Importance of Adverse Event Reporting:

Pharmacovigilance for herbal and alternative medicines relies on adverse event reporting by healthcare professionals and consumers to ensure safety. This is important for:

1. Identifying safety concerns: Adverse event reports help detect potential safety issues with herbal products, enabling prompt action.
2. Assessing benefits and risks: Collecting adverse event data helps evaluate the benefits and risks of herbal medicines, informing healthcare decisions.
3. Ensuring quality: Robust quality control measures, such as GMP and proper labelling, are crucial to ensure the safety and efficacy of herbal products.
4. Informing consumers: Transparent adverse event reporting educates consumers about potential risks, enabling informed choices.
5. Guiding regulatory decisions: Pharmacovigilance data informs regulatory decisions on product safety, labelling, and approval.[22]

Regulations for herbal products vary globally, with some countries having stricter standards than others. For example:

In the US, dietary supplements are regulated by the FDA, but with less stringent standards than pharmaceuticals.

Some European countries have more rigorous regulations for herbal products.

Effective pharmacovigilance is essential to ensure the safety and efficacy of herbal and alternative medicines.[23]

Concept of Integrative Pharmacovigilance:

Integrative pharmacovigilance represents an innovative strategy designed to monitor adverse events (AEs) across various therapeutic modalities, including pharmaceuticals, herbal medicines, and nutraceuticals. This approach acknowledges the interconnectedness of therapies and advocates for a "One Health" perspective regarding drug safety.

Key Components of Integrative Pharmacovigilance include:

1. Uniform AE Reporting Systems: Implementation of standardized reporting systems to collect and analyse AE data from diverse sources.
2. Data Integration from Multiple Health Systems: Integration of data sourced from electronic health records, claims databases, and additional healthcare systems.
3. Harmonized Regulations and Collaboration: Fostering collaboration among regulatory authorities. [24,25]

Need of Integrative Pharmacovigilance:

The adoption of integrative pharmacovigilance enables healthcare professionals, regulatory agencies, and industry stakeholders to collaboratively identify potential risks and interactions, promote safer usage, and enhance public health safety. A multidisciplinary approach that incorporates expertise from pharmacology, toxicology, botany, and traditional medicine is crucial for effective integrative pharmacovigilance. By merging conventional and traditional medicine, integrative pharmacovigilance can inform regulatory decisions, advance evidence-based medicine, and ensure the safe and effective use of herbal nutraceuticals alongside conventional therapies. Given the increasing use of herbal nutraceuticals, integrative pharmacovigilance is poised to play a significant role in safeguarding public health.

To achieve this objective, the following actions are essential:

1. Develop Standardized Reporting Systems: Establish uniform reporting protocols and databases to facilitate the collection and analysis of adverse event data.
2. Enhance Collaboration: Foster partnerships among healthcare professionals, regulatory agencies, industry stakeholders, and patients to promote the sharing of information and best practices.
3. Increase Awareness: Educate healthcare professionals and patients regarding the potential risks and benefits of herbal nutraceuticals to encourage reporting and informed decision-making.
4. Support Research: Conduct studies on the safety and efficacy of herbal nutraceuticals to provide valuable insights that can inform regulatory decisions.

By implementing these strategies, integrative pharmacovigilance can serve as an effective tool for ensuring the safe and effective use of herbal nutraceuticals and conventional therapies, ultimately contributing to the protection of public health.[26]

Benefit of Integrative Pharmacovigilance:

1. Enhanced Patient Safety: Integrative pharmacovigilance facilitates comprehensive monitoring of adverse events, thereby mitigating risks and improving patient outcomes.

2. Improved Signal Detection: The implementation of standardized reporting and data integration enhances the identification of safety signals and potential interactions.
3. Comprehensive Safety Monitoring: The monitoring of adverse events across various therapeutic modalities offers a holistic view of safety profiles.
4. Increased Efficiency: The optimization of reporting and data analysis minimizes redundancy in efforts and enhances resource utilization.
5. Better Regulatory Decision-Making: The alignment of regulations and collaborative efforts support informed decision-making and policy formulation.
6. Enhanced Public Health: Integrative pharmacovigilance encourages a proactive stance on drug safety, contributing to better public health outcomes.
7. Reduced Healthcare Costs: The early identification and prevention of adverse events lead to decreased healthcare expenses associated with adverse reactions.
8. Increased Transparency and Trust: Standardized reporting and collaborative efforts promote transparency, thereby fostering trust among stakeholders.
9. Improved Research and Development: Integrative pharmacovigilance provides valuable insights for research and development, facilitating the creation of safer and more effective therapies.
10. Global Harmonization: Collaborative initiatives among regulatory authorities advance the global harmonization of pharmacovigilance practices.[26]

Impact:

1. Patient-centred care: Integrative pharmacovigilance emphasizes the importance of patient safety and well-being.
2. Risk management: It employs a proactive approach to the identification and mitigation of risks.
3. Innovation: This framework fosters the development of safer and more effective therapies.
4. Public health policy: It provides critical insights that inform policy decisions and promote evidence-based practices.
The adoption of integrative pharmacovigilance enables stakeholders to collaborate in enhancing patient safety, improving public health outcomes, and fostering a culture of safety within the healthcare industry. Collaborative efforts between industry stakeholders and academia are essential for the development of harmonized guidelines and standards. [27]

Importance of Integrative Pharmacovigilance

Integrative pharmacovigilance plays a vital role in ensuring the safety and efficacy of herbal, nutraceutical, and conventional therapies. By monitoring adverse events (AEs), regulatory agencies can identify potential safety concerns, assess the benefit-risk balance of products, and make informed decisions regarding product safety, labelling requirements, and market authorization. Additionally, integrative pharmacovigilance fosters transparency and accountability, empowering consumers to make informed healthcare choices while enhancing their confidence in the safety and efficacy of their medications.[22]
Through its dynamic evolution and the adoption of advanced technologies, pharmacovigilance remains at the forefront of identifying, understanding, and mitigating adverse drug reactions, driven by a steadfast commitment to protecting patients and promoting excellence in healthcare.[28]

Future Prospects of Integrative Pharmacovigilance:

The future of integrative pharmacovigilance for monitoring adverse events associated with herbal nutraceuticals and conventional therapies appears promising, supported by advancements in technology, regulatory harmonization, and collaboration. The following are key developments that will influence this future:

Key Trends:

Artificial Intelligence (AI) and Machine Learning (ML): AI-driven tools will improve pharmacovigilance by automating the detection of adverse events, analysing extensive datasets, and predicting potential safety signals.
Real-World Evidence (RWE) Integration: RWE sourced from patient registries, healthcare databases, and wearable devices will offer valuable insights into the long-term safety and effectiveness of treatments.

Digital and Real-World Data Utilization: The use of digital health records and electronic patient databases will broaden the scope of pharmacovigilance, facilitating real-time monitoring and data analysis.
Global Regulatory Harmonization: International collaborations will lead to the standardization of pharmacovigilance guidelines, ensuring consistent drug safety standards across the globe. [22]

Opportunities:

Underreporting of Adverse Events: Encouraging healthcare professionals and patients to report adverse events will remain a challenge.
Data Overload and Signal Detection: AI-driven tools will help distinguish meaningful safety signals from irrelevant information.
Regulatory Compliance Complexity: Harmonizing regulations globally will facilitate compliance and efficient drug monitoring. [29,30]

Future Directions:
AI-Enabled Automated Drug Safety Monitoring: Predictive analytics and automation will enhance efficiency and accuracy in detecting drug-related risks.
Expansion of Pharmacovigilance Workforce: Specialized training programs will equip professionals to meet evolving regulatory standards.
Blockchain for Secure Data Management: Blockchain technology will ensure secure, transparent, and tamper-proof recording of pharmacovigilance data.[31]

Conclusion:

By embracing integrative pharmacovigilance, we can optimize the safety and efficacy of herbal nutraceuticals and conventional therapies, ultimately enhancing patient care and public health. This approach holds significant promise for reducing adverse events, improving treatment outcomes, and fostering a more informed and collaborative healthcare environment.

References:

1. [1] Mann, R.D., Andrews, E.F. (Eds.), 2002. Pharmacovigilance. Wiley, Chichester. McLernon, D.J., Bond, C.M., Hannaford, P.C., et al., 2010.Adverse drug reaction reporting in the UK. Drug Safety 33
2. [2] Ackernecht, E.H., Therapeutics from the Primitives to the Twentieth Century. Hafner Press, New York, 1973.
3. [3] Gossell, M., Simon, O.R., West, M.E., The past and the present use of plants for medicines. West Indian Medical Journal, 2006, 55:217.
4. [4] Shaw, D., 2010a. Toxicological risks of Chinese herbs. Planta Medica 76, 2012–2018.
5. [5] Perharic, L., Shaw, D., Leon, C., De Smet, P.A., Murray, V.S., 1995. Possible association of liver damage with the use of Chinese herbal medicine for skin disease. Veterinary and Human Toxicology 37, 562–566
6. [6] Nortier, J., Vanherweghem, J.L., 2007. For patients taking herbal therapy – lessons from aristolochic acid nephropathy. Nephrology Dialysis and Transplantation 22, 1512–1517
7. [7] Choudhury A, Singh PA, Bajwa N, Dash S, Bisht P. Pharmacovigilance of herbal medicines: Concerns and future prospects. Journal of Ethnopharmacology. 2023 Jun 12; 309:116383.
8. [8] https://mjpharm.org/adverse-effects-of-herbs-and-drug-herbal-interactions/
9. [9] MacGregor, FB, Abernethy VE, Dahabra S. Hepatotoxicity of herbal remedies. BMJ 1989; 299:1156-1157.

10. [10] https://link.springer.com/chapter/10.1007/978-981-99-0677-2_15
11. [11] https://www.sciencedirect.com/science/article/abs/pii/B9780128210383000690
12. [12] https://www.onlymyhealth.com/nutraceuticals-benefits-side-effects-1630138486
13. [13] https://pmc.ncbi.nlm.nih.gov/articles/PMC3780488/
14. [14] Schäfer T, Riehle A, Wichmann HE, Ring J. Alternative medicine in allergies – prevalence, patterns of use, and costs. *Allergy* 2002; **57**: 694–700.
15. [15] Review article Challenges and opportunities of integrating traditional medicine into healthcare systems.
16. [16] WHO. (2005b). *National Policy on Traditional Medicine and Regulation of Herbal Medicines*. Report of a World Health Organization Global Survey. Geneva, Switzerland: WHO [Google Scholar]
17. [17] Zhou J., Ouedraogo M., Qu F., Duez P. (2013). Potential genotoxicity of traditional Chinese medicinal plants and phytochemicals: an overview. *Phytother. Res.* 10.1002/ptr.4942
18. [18] Li Y, Wu Y, Jiang T, Xing H, Xu J, Li C, et al. Opportunities and challenges of pharmacovigilance in special populations: A narrative review of the literature. Ther Adv Drug Saf 2023; 14:20420986231200746.
19. [19] Singh P, Vaishnav Y, Verma S. Development of pharmacovigilance system in India and paradigm of pharmacovigilance research: An overview. Curr Drug Saf 2023;18:448-64
20. [20] Sameena S, Shafi S. Necessity, importance, future aspects and challenges of pharmacovigilance. Asian J Pharm Res Dev 2022;10:110-9.
21. [21] Phougat P, Beniwal M, Kapoor G, Aggarwal N, Kumari A, Sharma R, et al. Role and responsibilities of various stage.
22. [22] Choudhury A, Singh PA, Bajwa N, Dash S, Bisht P. Pharmacovigilance of herbal medicines: Concerns and future prospects. Journal of Ethnopharmacology. 2023 Mar 12:116383.
23. [23] Linezolid (Zyvox) : severe optic neuropathy
24. [24] Bhosale Uma, Jaiswal Shruti, Yegnanarayan Radha and Godbole Gouri, "A Pharmacovigilance Study of Antiasthmatic Agents in Patients of Bronchial Asthma at a Tertiary Care Hospital", Journal of Clinical & Experimental Research, 1, May-August 2013, 26-30.
25. [25] Padmavathi G. V., Beere Nagaraju, Divakara P., Suresh Kumar P., Surendranath A. and Sunil R. Patel, "Screenplay of pharmacovigilance among nursing staff in Bangalore",2, February 2013, 365-370.
26. [26] Pharmacovigilance through phased clinical trials, post -marketing surveillance and ongoing life cycle safety. Chakraborty A, Venkatraman JV (Editors). In:The Quintessence of Basic and Clinical Research and Scientific Publishing. Springer Nature Publishers UK, 2023:427-42.
27. [27] Hall M, Mc Cormack P, Aurthur N, Feely J. The spontaneous reporting of pharmacology, 1995; 40: 173-175.
28. [28]https://www.lindushealth.com/blog/the-importance-of-pharmacovigilance-a-comprehensive-guide-to-understanding-and-detecting-adverse-effects#:~:text=Pharmacovigilance%20plays%20a%20crucial%20role,and%20helps%20maintain%20public%20health
29. [29] Graham, D. J., Campen, D., Hui, R., Spence, M., Cheetham, C., Levy, G., Shoor, S., & Ray, W. A. (2012). Risk of acute myocardial infarction and sudden cardiac death in patients treated with cyclo-oxygenase 2 selective and non-selective NSAIDs: Nested case-control study. The Lancet, 365(9458), 475–481. https://doi.org/10.1016/S0140-6736(05)17810-4
30. [30] Shah, R. R., Smith, R. L., & Jones, R. (2015). Personalized medicine: Challenges and opportunities. British Journal of Clinical Pharmacology, 79(3), 321–336. https://doi.org/10.1111/bcp.12532
31. [31] https://iip.indoreinstitute.com/blog-post/the-future-of-pharmacovigilance-in-drug-safety-and-public-health/