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Pharmacovigilance

Volume 2

Edited by Charmy S. Kothari and Manan Shah

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Meet the editors

Dr. Charmy S. Kothari has more than 18 years of teaching and research experience. Her research interests include analytical and bioanalytical method development and validation, impurity profiling and stability studies, and isolation, identification, and characterization of marker compounds from plants and formulations. Her research also includes regulatory guidelines, registration procedures, evaluation and approval procedures of various regulatory agencies worldwide, and the pharmacovigilance system. She has published more than fifty research and review papers in reputed journals. She is a recognized postgraduate and Ph.D. guide at the Institute of Pharmacy, Nirma University, India. She received several research grants from government funding agencies like the Gujarat Council on Science and Technology (GUJCOST), Indian Council of Medical Research (ICMR), and Department of Science and Technology (DST), and an international travel grant from DST-SERB.

Dr. Manan Pareshbhai Shah completed his Ph.D. titled "A Data mining approach to comprehensive signal detection of later generation contraceptive drugs" from the Institute of Pharmacy, Nirma University under the guidance of Dr. Charmy Kothari. He received his Ph.D. award in Dec 2022. His main area of research is global pharmacovigilance systems and regulatory affairs. For his Ph.D. research work, Dr. Shah received a fellowship from the Indian Council of Medical Research (ICMR) as Senior Research Fellowship (SRF). He has attended various national and international conferences in India and abroad. His research aims to identify the toxic signal (class-specific) for contraceptive drugs for the safe and rational use of the drug with the application of statistical methods like Disproportionality Analysis. He is also investigating the present regulatory framework of pharmacovigilance in India to identify the cognizance of pharmacovigilance among healthcare professionals. He is currently associated with a leading pharmaceutical company in India.

Contents

Preface

No matter how elaborate the preclinical and clinical phases of drug development are before a drug is approved, unless the drug hits the market and is in efficient use, its safety information is not fully elucidated. This is where signal detection in pharmacovigilance comes in. Signal detection is the process of using statistics and other data to determine new or changing risks of drugs. If a drug is approved for the market, this means that it showed a positive or predominating benefit-to-risk ratio that satisfied the relevant medical and statistical criteria. However, meeting such criteria does not mean that the drug's safety profile or "signal" is fully determined. A quantitative signal detection is a promising approach that helps in the early identification of new, rare reactions (desired or undesired) of a drug. Determining the safety information of marketed medicines is a continual process. Pharmacovigilance was the first method developed for post-marketing surveillance, and despite its inherent limitations such as lack of information or underreporting, it is still the main method for determining drug safety. This book presents a comprehensive overview of pharmacovigilance and signal detection.

The editor would like to thank all the authors for their excellent contributions.

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Section 1

Pharmacovigilance

Chapter 1

Introductory Chapter: Pharmacovigilance Regulatory Framework of Three Asian Countries – South Korea, Singapore and Thailand

Apoorva Kulkarni, Charmy S. Kothari, Manan Shah and Rajvi Patel

1. Introduction

PV has established itself as a huge and dynamic working field for health-related workers since it involves major fields like operations, surveillance, systems and qualified person for pharmacovigilance. Each field has a complex but interrelated role.

PV is the call for the era since the clinical trials are increasing in number day by day, and the safety concerns for drugs are becoming larger and larger. PV is an immediate requirement for every country for the following reasons:

- Number of drug recall cases are ascending.
- Safety data collected during preclinical and clinical studies is insufficient to support real-world evidence.
- Detection of the rarest of adverse reactions due to a limited sample size of clinical trial phases is very challenging.
- Lack of knowledge related to vulnerable groups which are excluded from trials such as infants, children, elderly, pregnant, breastfeeding and lactating women.
- Polypharmacy in practice.
- Lack of consideration of patient's state like comorbidities, drug–drug interaction and drug–food interaction.
- Lack of adherence to medications.
- Lack of awareness among patients, healthcare professionals pharma companies and regulatory agencies regarding PV and drug safety-related challenges.

The above factors make PV more significant as there is voluminous data to be reported, collected and analysed and this requires a team of subject matter experts who can effectively detect risks related to drugs and assist in maintaining the drug into the market throughout its lifecycle by constantly updating their risk management plans for patients' safety and well-being.

Asia is a continent which embraces a range of cultural, geographical and medical practices. Thus, it is a challenge to unify and standardize pharmacovigilance in Asia. The West is more advance in relation to the concept of Pharmacovigilance while Asian countries still lag behind. As a result of the rapid increase in clinical trials and clinical research activities in Asia, there is a great need to identify and implement effective pharmacovigilance practices.

2. Current pharmaceutical market in Asia

The following are the trends as of 2022 that the selected countries under study observe (**Table 1**) [1].

A 4% of global drug development pipelines are being witnessed by companies of Korea having 900 new medicines under development [2].

World Bank data in 2012 stated that Singapore expends 4.7% of its GDP into the healthcare industry. In Singapore on annual basis, the pharmaceutical industry subsidizes over 85% of the total biomedical sciences manufacturing yield. According to World Health Organization (WHO), the healthcare system of Singapore holds the sixth position globally [3].

Similar to various countries in Asia such as China, Korea and Japan, the population in Thailand is also facing rapid ageing. Over 20% of Thailand's population will be older than 60 by 2025. The threat of developing respiratory diseases, cancer and diabetes increases with age there will be a higher demand for newer and better pharmaceutical products in Thailand [4].

3. Pharmacovigilance regulatory framework of South Korea

The spontaneous reporting system for ADR in Korea was started by the Korea Ministry of Food and Drug Safety (MFDS) in 1988. Korea entered the WHO-UMC in 1992 and has been involved in international drug monitoring since then. Since 1995, Korea initiated a re-examination of the safety of newly approved drugs, that is postmarketing surveillance. The year 2000 witnessed enabling of web-based reporting as a system for adverse event reporting. Since 2003, all manufacturers and pharmacists have been required to report all adverse drug reactions (ADRs) to the

Country	Pharmaceutical market size (billion)	Anticipated growth rate (%)	Population (in millions)
South Korea	$16.43	4.89	51
Thailand	$2.41	1.07	69
Singapore	$1.56	6.25	5.6

Table 1.
Market statistics for selected countries.

MFDS within 15 days of the incidence of the ADR. In 2006, the Ministry of Food and Drug Safety (MFDS) declared three university hospitals as Korean Regional PV Centers (RPVCs) to promote spontaneous ADR coverage. In 2007, it became mandatory for all pharmaceutical companies to appoint responsible persons for PVs (RPPV). A well-established PV network was constructed in 2009 including 15 RPVCs across Korea. A national concurrent Medication Use Review system, which covers drug-drug interactions and drug-age contraindications and is a real-time screening system, was developed in 2010 for both physicians and pharmacists. Korea Institute of Drug Safety and Risk Management (KIDS) was created under the MFDS in April 2012, based on the Pharmaceutical Affairs Law' Article 68-3.

In 1988, Korea MFDS launched in Korea the Adverse Drug reaction reporting system. Since then, healthcare providers and patients have been reporting spontaneous ADRs. Despite of first 10 years of lower reporting rates, Korea has managed to accelerate the same after the establishment of KIDS (Korea Institute of Drug Safety and Risk Management) in 2012. Thus KIDS has majorly contributed to Korean Pharmacovigilance.

Healthcare providers, consumers, RPVCs, consumers and pharmaceutical companies are all required to submit reports to KIDS. RPVCs are managed by KIDS and serve a variety of functions, including data collection and causality evaluation on ADR results. It offers drug safety education and serves as a drug awareness hub.

KIDS detects signals by employing the WHO-UMC scale. It also employs a number of data mining techniques, including Bayesian Confidence Propagation Neural Networks. The detection of potential signals can lead to specific regulatory decisions, such as label updates. For a more detailed study of drug usage and disease occurrence, data mining approaches are being extended to include the use of the HIRA database and hospital electronic medical record (EMR) databases.

KIDS is also in charge of determining causality, using a variety of algorithms based on decision criteria such as challenge, dechallenge and rechallenge data, as well as previous bibliographic details and other aetiologic alternatives. For causality evaluation and signal confirmation, pharmacoepidemiologic approaches such as cross-sectional,

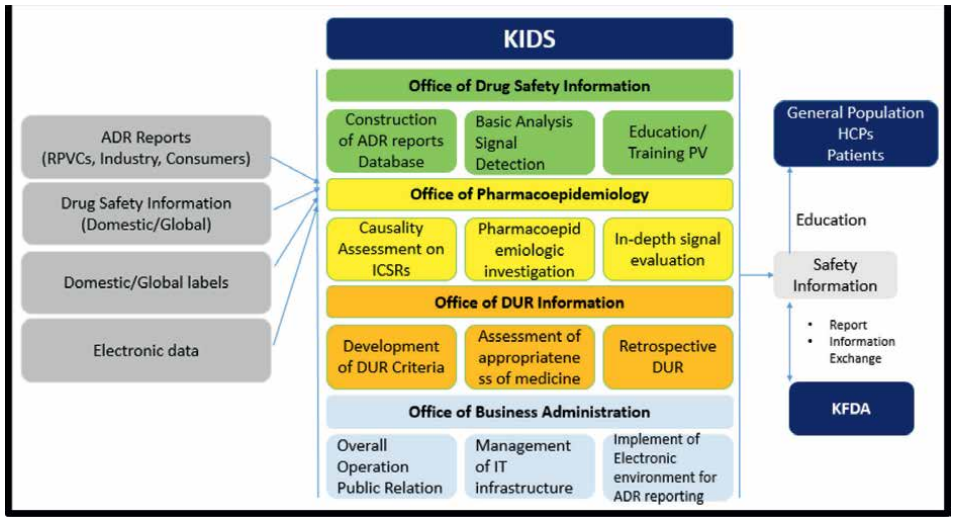

Figure 1.
Flowchart depicting various drug safety information in kids [5].

case-crossover, case–control and other cohort studies are used. A Data Utilization Review is well dictated as an "authorized, structured, and continuing program that reviews, analyzes, and interprets patterns of drug usage in a given health care delivery system against predetermined standards."

The Drug Utilization Review (DUR) was created to reduce prescription errors and improve pharmaceutical treatment quality. A DUR informs doctors and pharmacists of the potential for adverse effects of their medications on patients.

Multiple databases, including the Korea ADR report database, HIRA (Health Insurance Review and Assessment Service) claims database, national mortality database, hospital EMR (Electronic Medical Record) database and cancer registry database, will be linked by the Korean national ADR monitoring system. ADR control programmes, such as the US FDA's Sentinel Initiative, will use big data in the near future. A drug injury relief initiative will be introduced, with the aim of determining the causality of adverse drug events.

Thus South Korea after 2012 with the help of KIDS has excellently flourished their pharmacovigilance systems (**Figure 1**) [5–8].

4. Pharmacovigilance regulatory framework of Singapore

In 1993, Singapore created the pharmacovigilance unit (PVU) [formerly known as the Adverse Drug Reaction Monitoring Unit (ADRMU)]. In 1994, the unit became the WHO's 40th member of the WHO International Drug Monitoring Program for international drug safety cooperation. In Singapore adverse event monitoring of therapeutic products is done by their drug regulatory authority, Health Science Authority. Spontaneous Reporting of the adverse event can be done for therapeutic products, vaccines, complimentary therapeutic goods like traditional medicines, Chinese proprietary medicines, health supplements, cell tissue gene therapy products, cosmetics and medical devices as well by patients, healthcare professionals and industry to the HSA. Adverse events that are eligible to be reported are as follows:

- All adverse effects associated with the use of new health products, defined as those that have been on the market for less than 5 years in Singapore.
- Any and all serious negative incidents, even though they are well-known.
- Unexpected adverse effects that are not in line with the product's packaging insert or labelling.

Healthcare professionals (HCPs) can report adverse events electronically (report online or mobile-friendly e-form), or manually by filling out unique colour-coded forms and mailing them to the HSA's Vigilance and Compliance Branch, Health Product Regulation Group, or sending an email to HSA productsafety@hsa.gov.sg.

- YELLOW FORM: therapeutic drugs and complimentary therapeutic products.
- BLUE FORM: vaccines.
- GREEN FORM: advanced therapeutic products.

Therapeutic product importers, distributors, retailers and registrants are all expected to disclose all serious adverse effects associated with their goods. The following information is needed for the initial report submission:

- An identifiable reporter or healthcare professional.
- An identifiable patient.
- An adverse effect.
- A suspected product.

Companies must fill out the Council for International Medical Science (CIOMS)-I form and send it to HSA via online report or email to report adverse events. If any applicable additional information on the related AE is requested, follow-up reports must be submitted within 15 calendar days on any previously submitted AE report. A medicinal products manufacturer, importer or registrant must keep track of any adverse events (AEs) that occur as a result of using the product and provide those records to HSA for inspection when requested. The record must be held for at least 2 years after the medicinal product's expiration date.

Companies are required to submit a Risk Management Plan for their therapeutic products (mandatory for NDA-1 and biosimilar applications and on case to case basis as decided by Health Science Authority (HAS) for New Drug Application 2/3 (NDA2/3), Major Variation Application OR Generic Drug Application). In addition to RMP, the company has to submit a Periodic Benefit-Risk Evaluation Report (PBRER) to HAS.

HSA can guide a registrant of a therapeutic product to implement a risk management plan that includes, but is not limited to, the following to mitigate risks related to unsafe and ineffective use of therapeutic products:

- Educational materials: Production and Distribution;
- Safety information: Production and Distribution;
- Clinical study performance of the therapeutic product;
- Active monitoring programmes of the therapeutic product;
- Programs to limit the therapeutic product's supply'

In order to improve the benefit-risk balance of therapeutic goods, additional RMAs are needed for those with significant known or potential risks that involve an extra level of risk minimization. This could include, but are not limited to:

- The company provides educational materials to physicians.
- Provision of patient medication guide by the company.

- Dear Healthcare Professional Letter Issuance.
- Restricted Access Programme (RAP) Implementation.
- Implementation of regulated distribution, for example, selected physicians/specialists/pharmacies supply.
- Pregnancy prevention programme implemented.

Causality assessment is done by HCPs using the following terms as per WHO UMC Causality Assessment Scale:

- definite,
- probable,
- possible,

Information types	Description of adverse events	Timeframe for reporting	Submission to
Spontaneous local adverse effect reports	Serious adverse reactions	Initial and follow-up reports must be submitted within 15 calendar days of the company's first knowledge.	VCB
	Non-serious AEs	On a regular basis, it is not necessary. However, records must be kept and produced for review when required.	—
Spontaneous foreign reports	Serious and non-serious AEs	On a regular basis, it is not necessary.	—
Risk management plans (RMPs)	For new drug applications form 1 (NDA-1) and biosimilar applications, RMP documents must be submitted. The following documents are included in the RMP: (1) an annex that is unique to Singapore, (2) the most recent version of the EU-RMP and/or US REMS that have been accepted (where available), (3) materials for a local RMP proposal	RMP documents should be included in the NDA-1 and biosimilar application dossiers application.	TPB
Periodic benefit–risk evaluation reports (PBRERs)	For selected products only	For a period of 2 years, at 6-month intervals, beginning on the date of approval of the therapeutic product or its international birth date and continuing annually for the next 3 years.	TPB

TPB: Therapeutic Products Branch; VCB: Vigilance and Compliance Branch.

Table 2.
Summary of safety reporting requirements.

- likely, and
- unconfirmed.

Data mining techniques are not disclosed by HSA on their official website.

Details regarding possible local adverse effects of therapeutic drugs and medical products can be found in the HSA Adverse Case Online Database, which is based on documentation submitted to them by healthcare practitioners and businesses [6, 9, 10].

- The HSA AE Online Enquiry e-service is available to industry partners.
- The Ministry of Health website provides links to healthcare professionals (**Table 2**).

5. Pharmacovigilance regulatory framework of Thailand

Thailand's pharmacovigilance system was developed in 1983. The Food and Drug Administration founded the national centre, which has a primary focus on the ADR monitoring programme. Starting with 176 total reports from many tertiary hospitals in the first year, the number of reports has grown to more than 50,000 each year, with pharmacists serving as the primary reporter. Consumers, market authorization holders and health services, such as drug stores, physician offices, private hospitals and all types of public hospitals, ranging from community hospitals to tertiary hospitals to academic and research hospitals, are also included in the field of work.

Together with other Asian nations, United States Agency for International Development (USAID) has taken the initiative to assess the pharmacovigilance mechanism in Thailand. The project's knowledge and learning experiences support not only the countries being examined, but they can also provide a base and principles for other countries' pharmacovigilance systems. Pharmacovigilance activities laws are as follows:

- The Policy, Laws and Regulations in Thailand are Drug Act (1967).
- National Drug Policy (2011) Strategy on National Drug System Development 2012–2016.

The name of the regulatory authority/website is the Thai Food and Drug Administration (www.fda.moph.go.th).

Thailand has officially joined the WHO programme (1984). For ICSR documentation, it uses the E2B compliance INTDIS format. WHO-ART (Adverse Reaction Terminology) was used for ADR terminology, ATC code for medication and ICD-10 for indication in medical terminology.

The type of reports in the PV database are as follows:

- Spontaneous reports,
- Reports of Adverse Event Following Immunization,
- Reports of Active Surveillance,

- Reports of Product Quality,
- PSURS, and
- Reports from PHPS.

The reporting odd ratio (ROR), which has been in use since 2006, is one of the quantitative methods used in signal generation.

Thailand has the provision of keeping the responsible person to submit reports according to drug categories

1. Convention and traditional medicines;
2. Medicines for compassionate use, and;
3. Narcotics and Medicinal Neuropsychotropic substances.

Adverse drug event reporting systems in Thailand are as follows:

1. AE – online reporting system which is available on their website with or without CIOMS form.
2. Thai FDA adverse event reporting form with or without the CIOMS form by supporting the report via fax, e-mail or mail to HPVCTHAI FDA Adverse Event Reporting CIOMS Form [11–16] (**Table 3**).

S. No.	Type of adverse event	Period allowed to submit initial report	Period allowed to submit follow-up report
1.	Death	1. Cause of death from • Vaccines • New drugs or new biological products with conditional approval (NC)/(NBC) • Unexpected/unlabelled ADRs Notify the Thai FDA immediately, for example, by fax or email **within 1 business day** after the first acknowledgement and submit a complete report within 7 days. 2. Other causes Notify the Thai FDA within 7 days and submit a complete report within 8 days.	Submit a report within 15 days whenever receiving additional information.
2.	Serious	Within 15 days	Submit a report within 30 days whenever receiving additional information.
3.	Non-serious	Within 2 months	Submit a report within 2 months whenever receiving additional information.

Table 3.
The following are the timeframes needed to be followed by industries for Adverse Drug Reporting.

6. Comparative analysis of pharmacovigilance regulatory framework of South Korea, Singapore and Thailand

Comparative parameters of pharmacovigilance regulatory framework of South Korea, Singapore and Thailand is shown in below table [12].

Parameters	South Korea	Singapore	Thailand
PV regulations	Pharmaceutical Affairs Act, MFDS Notification Article 2013-118	Health Products Act and Health Products (Therapeutic Products) Regulations 2016	Drug Act (1967) National Drug Policy (2011) Strategy on National Drug System Development 2012–2016
Mandatory industry reporting of serious ADRs	Yes	Yes	Yes
Clinical trials register exists?	Yes (CRIS)	Yes (clinical trial register)	Yes (Thai clinical trials registry)
Monitoring period for new drugs required	Yes (4–6 years)	Yes (5 years)	YES (at least 2 years)
Expedited reporting of serious ADRs for marketed drugs required	15 days	15 days	15 days
PV inspections and audits required	Yes	No. However, in relation to the manufacture of the therapeutic product, compliance with the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Cooperative Scheme (PIC/S) Guide to Good Manufacturing Practice (GMP) for Medicinal Products is required	Yes
Spontaneous reporting database exists	Korea Adverse Event Reporting System (KAERS)	HSA Adverse Event Online Database	Thai Vigibase
Periodic safety update reports required (frequency)	Yes (for the first 2 years, every 6 months and then annually for the next 3 years) (total: for the first 5 years)	Yes. PBRER* is a term used in Singapore (for an initial period of 2 years, at intervals of 6 months commencing from either the date of registration of the therapeutic product or its international birth date; and annually, for the next 3 years)	Required when requested by Thai FDA
Provision of risk mitigation plan	Yes	Yes (Singapore Specific Annex available)	Yes
Provision of PMS supervisor	No	No	No

Parameters	South Korea	Singapore	Thailand
Re-examination period	Yes	No	No
Qualified personnel pharmacovigilance	Yes	Yes (contact person)	Yes (responsible person)
Challenges	The WHO-ART code is used to code adverse events in KAERS results. Korea will begin using the MEDRA scheme in 2020.	Patient information is obtained in a variety of data environments and formats. The knowledge extracted into NEHR may not be in a coherent codified structure due to the complexities of data stored in the different modules. Additional data cleaning (e.g. manually converting free text data to structured data) is both time-consuming and repetitive	The Thai Vigibase generates established drug-ADR signals on a regular basis, but new signals are rarely produced.

7. Conclusion

Asia is the world's fastest-growing pharmaceutical market, with enormous potential for drug discovery and marketing. As a result, pharmaceutical regulations in this area are attracting a lot of interest from pharmaceutical companies all over the world. In Asia, pharmaceutical and drug registration is becoming more regulated. Although pharmacovigilance systems in all three countries listed above have made significant progress in recent decades. All pharmacovigilance systems face a common set of ongoing challenges in drug safety surveillance in one of five major interrelated areas: engaging the public, collaborating and partnerships, incorporating informatics, adopting a global approach and assessing the impending danger. These difficulties are not fresh in general. Last but not least, high-level training to increase trained manpower and raising awareness among consumers and HCPs to report as many ADRs as possible would aid in the development of a strong PV system in Asia.

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Chapter 2

Stakeholders in Pharmaceutical Policy Development

Mohammad Ishaq Geer

Abstract

Pharmaceutical policy development is a linear and step-wise process that moves from problem statement or agenda setting, to planning and analysis, to definitions and objectives, to policy formulation and statutory approval, to implementation and monitoring, to policy review and evaluation and finally to improvisation. In the process of developing and implementing such a policy framework several stakeholders including national and multi-national drug manufacturers, state and central governments (including all ministries like health, commerce, trade, industry), regulatory authorities, patients, doctors, pharmacists, pharmaceutical traders, insurance agencies, academia, professional associations, NGOs, civil society and consumer groups assume primary importance without whose active involvement the whole process would be inadequate and sometimes even inappropriate leaving huge gaps in their comprehensiveness, inclusiveness and acceptability. This chapter defines the role and describes the importance of these very stakeholders in the process of pharmaceutical policy development and implementation in any settings across the world.

Keywords: academia, civil society, consumer groups, doctors, drug regulators, evaluation and monitoring, NGOs, patients, pharmaceutical industry, pharmaceutical policy development, pharmaceutical traders, pharmacists, policy implementation, professional associations, stakeholders

1. Introduction

Essentially pharmaceutical policy formulation can be viewed from three different perspectives viz., supply chain perspective that includes components like selection, quantification, tendering and procurement, storage and distribution, quality control and use by the patients; industrial perspective that includes components like manufacture, sale, import, export, licensing, pricing, investments, R&D including clinical research, innovation, patents and drug regulatory affairs; rational use perspective that includes components like safety, efficacy and quality of medicines; promotion of accessibility (including availability and affordability), rational prescribing, rational dispensing and rational use of medicines besides provision of cost-effective, timely and efficient centralized procurement and decentralized distribution of drugs. In spite of different perceptions and perspectives about pharmaceutical policy it goes without saying that quality pharmaceutical and healthcare services to patients can

only be ensured in presence of a strong policy framework that caters to all the needs in respect of drug delivery services and incorporates all components required to enforce and implement existing laws in respect of key issues of public importance.

Worldwide, at national levels terms like national drug policy, national medicines policy and national pharmaceutical policy are used synonymously to describe a policy framework for action in relation to import, export, pricing, investments, research and development, industrial licensing and manufacture of drugs and pharmaceuticals though at deeper regional levels these terms more often than not are used to indicate policies required to enforce and ensure effective quality control of drugs; rational prescribing and use of medicines; availability of safe and effective drugs in adequate quantities particularly at government health facilities; improved procurement, storage and distribution practices for drugs and other medical supplies; quality pharmaceutical and healthcare services at hospitals; stringent enforcement of drug related laws; adequate pharmacy and health education, research and training facilities at all academic and healthcare institutions etc.

Thus at regional and state levels focus of pharmaceutical policy development is more upon regulating safe and effective use of good quality drugs, good dispensing and prescribing practices and rational use of medicines by the patients besides their availability at affordable prices to all sections of the society irrespective of their caste, creed, color or religion within one hour walking distance from their place of inhabitation as well as their acceptability as a reliable source of relief from diseases and disorders. WHO defines national medicines policy as a commitment to a goal and a guide for action that expresses and prioritizes the medium- to long-term goals set by the government for the pharmaceutical sector, and identifies the main strategies for attaining them. It provides a framework within which the activities of the pharmaceutical sector can be coordinated. It covers both public and private sectors, and involves all the main actors in the pharmaceutical field [1].

On paper, the policy development process appears to be a linear process. It is a step-by-step process that moves from problem statement, to definition, to objectives and outcomes. Those objectives and outcomes are developed, analyzed and evaluated into optional solutions and instruments to be deliberated on. A decision is made by elected or government officials. A policy moving forward goes into program design, potential legislative drafting, implementation and planning. The program is implemented, monitored and evaluated. Finally, the process is reviewed and assessed. The problem is that policy development does not happen in a vacuum. The process looks opaque from the outside in, (given policy priorities, urgencies and timelines) the actual policy process does not always follow the theoretical process, and while stakeholder/citizen engagement can happen throughout the policy cycle, it is at the discretion of the policy makers when, how and what impact it will have on the outcome [2].

In the process of developing and implementing a pharmaceutical policy framework several stakeholders including national and multi-national drug manufacturers, state and central governments (including all ministries like health, commerce, trade, industry), regulatory authorities, patients, doctors, pharmacists, pharmaceutical traders, insurance agencies, academia, professional associations, NGOs, civil society and consumer groups assume primary importance without whose active involvement the whole process would be inadequate and sometimes even inappropriate leaving huge gaps in their comprehensiveness, inclusiveness and acceptability.

A national drug policy, presented and printed as an official government statement, is important because it acts as a formal record of aspirations, aims, decisions and commitments. Without such a formal policy document there may be no general

overview of what is needed; as a result, some government measures may conflict with others, because the various goals and responsibilities are not clearly defined and understood. The policy document should be developed through a systematic process of consultation with all interested parties. In this process the objectives must be defined, priorities must be set, strategies must be developed and commitment must be built. The consultations and national discussions preceding the drug policy document are very important, as they create a mechanism to bring all parties together and achieve a sense of collective ownership of the final policy. This is crucial in view of the national effort that will later be necessary to implement the policy. The policy process is just as important as the policy document itself [1].

Role, responsibilities and importance of various stakeholders in pharmaceutical policy development and implementation is described one-by-one as under:

2. Governments

Governments include state and central/federal governments and all its ministries concerned with the manufacture, import, export, investment, licensing, pricing, R&D and quality control of drugs. They are the key stakeholders and in fact pioneer in pharmaceutical policy development, planning, implementation and monitoring. For any new pharmaceutical policy development, initiatives must come from the governments and it is mainly their duty to take all other stakeholders on board for consultation before promulgation of any policy framework. Political will of the government can be the real game-changer in any country for development of effective policies on quality control, procurement, distribution, safe and effective use of medicines alongwith their equitable access, affordability and financial risk protection. Political will of the federal and state governments alone can ensure full transparency and accountability in drug selection, quantification, procurement, tendering, distribution and rational use and for such a will to take shape strong and effective leadership and governance structure is a pre-requisite. Some of the most robust policy documents have eventually turned to be a failure in absence of political will, support and effective leadership of central and state governments. Supportive governments and willing political establishments alone can earmark sufficient budgetary allocations towards healthcare in order to sufficiently meet drug demands and bear all administrative costs besides giving full autonomy to the procurement agencies to follow norms and well-established standards in drug quality and procurement without any kind of government or political interference.

India presents a peculiar example of how different federal ministries govern different aspects of pharmaceuticals and therefore how they need to be consulted and integrated not only for developing an effective policy framework but also for its effective implementation and constant monitoring. In India Ministry of Chemicals and Petrochemicals oversees policy, planning, development and regulatory activities pertaining to the chemicals, petrochemicals and pharmaceuticals sector whereas Ministry of Health and Family Welfare examines pharmaceutical issues within the larger context of public health and the focus of the Ministry of Chemicals and Fertilizers is on the industrial policy. Other ministries that also play a role in the drug regulation process include the Ministry of Environment and Forests, Ministry of Finance, Ministry of Commerce and Industry and the Ministry of Science and Technology. Issues related to industrial policy such as the regulation of patents, drug exports and government support to the industry are governed by the Department

of Industrial Policy and Promotion and Directorate General of Foreign Trade, both under the aegis of Ministry of Commerce and Industry and the Ministry of Chemicals and Fertilizers [3].

3. Drug regulators

Most important organ of the governments that are directly responsible for implementation and execution of the Acts, Ordinances, Rules and Regulations related to clinical trials, manufacture, import, export, licensing, sale, distribution, storage and dispensing of drugs are the drug regulators though they are not at the forefront of pharmaceutical policy development in many countries like India where that task is accomplished directly by the ministries themselves. However for any comprehensive, practicable and robust policy development drug regulators are very important stakeholders for they are the ones who implement policies on ground and are in know-how of the practical difficulties and hurdles in their implementation. Therefore without their consultation no policy document can be considered to be complete in all respects. That is the reason why in spite of being a government functionary drug regulators deserve a special mention as stakeholders in pharmaceutical policy development. On the basis of their past experience and practical knowledge they can be of immense help in giving significant inputs about the gaps, barriers, prospects and challenges towards adoption and implementation of new pharmaceutical policies like for instance universal health coverage policy, drug de-addiction policy, counter-spurious drug policy, effective pharmaceutical pricing policy, generic drug substitution policy, drug recall, disposal and withdrawal policy, drug procurement and medicines management policy etc.

Without the interest and active involvement of drug regulators quality assurance of medicines remains a far-fetched dream particularly in developing countries. This is illustrated by the very fact that India in spite of being a world leader in manufacture and supply of quality generic drugs to the extent that it covers 20–30 percent of the world market and is popularly known as the "pharmacy of developing world" yet a vast section of its own population to the extent of 50–65% was not having access to quality generics as per the World Medicines Situation Report [4]. However, the situation has drastically improved in recent years ever since Govt. of India implemented a whole lot of new Universal Health Coverage Schemes like Ayushman Bharat – Pradhan Mantri Jan Arogya Yojana (AB-PMJAY), Pradhan Mantri Jan Aushadhi Yojana (PMJAY) and many others. Unlike previous schemes, AB-PMJAY covers larger population, provides more comprehensive benefit package and incorporates a wider network of hospitals for healthcare delivery. Thus in spite of several universal health coverage policies like *Jan Aushadhi* (people's medicine) scheme, *Rashtiya Swasth Bhima Yojna* (National Health Insurance Scheme) and recently launched *Ayushman Bharat* (Long live India) having been launched in the past by the successive governments of India, quality and effectiveness of generic drugs supplied free of cost at government health facilities continued to remain doubtful and unreliable for a long time thereby affecting the overall success of these government schemes and primarily it was the failure of drug regulators in ensuring fool-proof quality assurance system. Paucity of government drug testing facilities, inadequacy of the drug inspectorate staff, insufficiency of the funds, manpower and equipments at govt. drug testing laboratories, less testing capacity and high testing load resulting into high lead time of testing, unscientific and unsystematic drug coding, sample handling and testing

procedures were some of the issues confronted in the quality assurance system of developing countries where drug regulators have a major role to play as important stakeholders in the pharmaceutical policy development and implementation.

4. Manufacturers

Pharmaceutical industry is the primary target of governments and their drug regulators when it comes to law enforcement and policy implementation. Doctors prescribe, pharmacists dispense and patients consume what manufacturers make available to them through ill or well-regulated markets and pharmaceutical supply chains. Therefore, manufacturers are the first to determine quality of medicines and thereby their effectiveness in alleviating the ailments of common masses. They are also the first to determine the prices of medicines and thereby their access to people living under various strata of the society. Hence manufacturers can play a lead role in ensuring health and well-being of the society by making good quality medicines available, affordable and accessible to all sections across the spectrum. However, it is a well-established fact that pharmaceutical companies are for-profit corporates whose primary goals are to enhance the worth of its share-holders. Therefore, they do not make all the drugs accessible to all the people irrespective of their paying capacity and that turns them into important stakeholders in pharmaceutical policy development because somewhere a balance has to be struck between access and profits, between investments and returns, between innovation and sustainability and between patents and patients.

Social justice in medical care demands that patients belonging to all sections of the society enjoy an equitable access to medicines irrespective of their caste, creed, color, religion, ethnicity, gender or paying capacity as enshrined under the principles governing universal healthcare, however, pharmaceutical corporates need money for research, development and innovation, major chunk of which is made available to them by either the academics or the governments from the tax-payers money as per the available facts and figures. Although the pharmaceutical industry emphasizes how much money it devotes to discovering new drugs, little of that money actually goes into basic research. Data from companies, the United States National Science Foundation, and government reports indicate that companies have been spending only 1.3% of revenues on basic research to discover new molecules, net of taxpayer subsidies [5, 6].

Cases of anti-cancer drugs Sovaldi and Imatinib and directly acting anti-viral drug used in Hepatitis-C, Sofosbuvir can be cited as classic examples of unreasonable and excessive profiteering by pharmaceutical corporates that eventually blocked access to these life-saving medicines in low- and middle-income countries and led to a spate of litigations following invoking of compulsory licensing provisions by the countries like India. Therefore, for any successful and sustainable pharmaceutical policy development pharmaceutical corporates need to be consulted and taken on board before arriving at any national medicines policy framework. This will ensure that the much-needed balance between profits and public demands, between money minting and patient-care, between corporate and social obligations and between patents and the public good is maintained.

With ever increasing obligations that pharmaceutical companies particularly the generic drug manufacturers have to fulfill as envisaged under various international trade agreements like TRIPS-plus (trade-related aspects of intellectual property right), FTA (free trade agreement), TPP (trans-pacific partnership), RCEP (regional comprehensive economic partnership) etc., it is becoming increasingly

difficult to indulge in trans-national trade of generic drugs owing to stringent patent regimes being invoked to protect innovations and intellectual property rights guaranteed under stiff patent regimes across nations. Several companies like Gilead are entering into trade negotiations and voluntary licensing agreements with indigenous generic manufacturers of countries with a view to restrict use of generic versions of patented drugs like Sofosbuvir locally and escape compulsory licensing provisions while at the same time protecting their data exclusivity privileges. Thus both generic and innovator product manufactures are important stakeholders in the development of any pharmaceutical policy framework related to import, export, pricing, R&D, investments, innovations and patents of medicines.

Doha Declaration on the TRIPS Agreement and Public Health adopted by the WTO Ministerial Conference of 2001 in Doha on November 14, 2001 reaffirmed flexibility of TRIPS member states in circumventing patent rights for better access to essential medicines. In Paragraphs 4 to 6 of the Doha Declaration, governments agreed that the TRIPS Agreement does not and should not prevent Members from taking measures to protect public health [7]. Accordingly, while reiterating their commitment to the TRIPS Agreement, WTO member states affirmed that the agreement can and should be interpreted and implemented in a manner supportive of their right to protect public health and, in particular, to promote access to medicines for all. Following this Declaration, at the end of 2015, United Nations Secretary-General Ban Ki-moon established a UN High-Level Panel on Access to Medicines with the mandate "to review and assess proposals and recommend solutions for remedying the policy incoherence between the justifiable rights of inventors, international human rights law, trade rules and public health in the context of health technologies". The scope of the work of the panel being global and ambitious is likely to address access challenges relating to access to medicines globally. At national level countries need to work on this policy incoherence between justifiable rights of inventors and public health by taking manufacturers and innovators on board during the process of policy formulation and implementation [8].

5. Healthcare personnel

Healthcare providers include prescribers, pharmacists and nurses who comprise the triad of patient-care and share a common interface with the end-users of medicines i.e., the patients. They are the primary stakeholders in ensuring rational prescribing, rational dispensing and rational use of safe and effective medicines in any settings. Irrespective of what kind of drugs are made available by the manufacturers and drug regulators in the market, doctors continue to be the pivots who choose on behalf of patients what drugs they must consume whereas pharmacists and nurses can ensure proper use of medicines through patient counseling and promote their adherence to the prescribed medications. Similarly well-informed and well-educated patients can ensure an appropriate use of medicines prescribed and thereby therapeutic outcomes and benefits of the pharmacotherapy can be maximized whereas their harms and risks can be minimized leading to a positive benefit-harm ratio.

Implementation of generic drug policies has faced several impediments and even stiff opposition from doctors, pharmacists and pharmaceutical traders in many countries as a result of certain perverse incentives offered by pharmaceutical companies through their sales promotion agents. Doctors often cite empirical evidence generated through years of experience in support of prescribing branded medicines and even

go to the extent of terming generic drugs as a big risk to their reputation owing to their perceived low quality and effectiveness. They also cite substitution of generics by unqualified and inadequately trained pharmacists as a reason to their skepticism towards prescribing generics. Their faith and belief in the quality and effectiveness of branded medicines seems to be as firm and unshakeable as their suspicion about the quality and effectiveness of generics.

It goes without saying that pharmaceutical companies spend heavily upon the promotion of branded medicines and offer huge financial incentives to doctors for prescribing the same that are often disproportionate and unjustified. That is the reason why WHO too has listed avoidance of perverse financial incentives as one of twelve core policies to promote more rational use of medicines [9]. No definite mechanism or regulations to curb unethical prescribing by doctors or to control unjustified distribution of exorbitant gifts by pharmaceutical companies are in place in many developing countries. Thus the aim of policy-makers should be to consult health-workers during the process of policy development seeking their cooperation and support in promoting generics, following ethical practices in drug promotion and prescribing, avoiding perverse incentives and instilling confidence for prescribing generics accompanied by an assurance to regulate their quality.

Pharmacists are critical to the medicines management process, yet are often largely detached from policy development. Logically, they should inform government policies which impact on their work or where their skills could be best applied to implement health care policy and medicines utilization in particular. It therefore becomes critically important that the pharmaceutical profession engages with national policy makers and in the strategic planning for health care [10]. Role of pharmacists assumes importance in observing good storage practices, good distribution and dispensing practices, efficient inventory control, demand forecasting and medication management practices, providing professional clinical pharmacy and pharmaceutical care services, drug and poison information services, offering patient counseling and promoting rational use of medicines besides ensuring drug safety through pharmacovigilance, adverse drug reaction monitoring and therapeutic drug monitoring services in all health system pharmacy settings. Of late pharmacist's role in social and administrative pharmacy, managed care and specialty care pharmacy including pediatric, geriatric, obstetric and palliative care has increased significantly. Similarly, nurses are responsible for ensuring administration of right drug to the right patient at the right time in its right dose and formulation. Together pharmacists and nurses can help a great deal in minimizing medication errors and other drug-related problems including inappropriate indication, unaddressed indication, inappropriate dose, duration or frequency of medication, drug interaction, adverse drug reaction, need for laboratory test or a compliance problem. While devising policy provisions for all these activities in consonance with the local needs and demands, due consultation with healthcare workers mentioned above can prove to be fruitful in addressing ground realities and concerns and evolving a framework that is best suited to the procedures and practices in vogue at the ground level.

One-size-fits-all approach is least likely to work in such matters as legislations vary from region to region and so do the roles, responsibilities and functions of pharmacists and nurses. While in most of the countries pharmacists are not legally authorized to prescribe medicines or make changes in the therapeutic regimen of the patients on their own, in some countries they can prescribe drugs as consulting pharmacists or assume full responsibility of patient's medication management as required for the practice of pharmaceutical care. In countries like India a qualified and trained

pharmacist can at best make a suggestion for a change in the therapeutic regimen to the patient's attending physician but cannot make any change in the prescription on his own thus considerably limiting his role in providing pharmaceutical care. This aspect needs to be kept in mind in pharmaceutical policy development vis-à-vis clinical pharmacy and pharmaceutical care services by qualified and trained pharmacists. Use of the terms "qualified" and "trained" is deliberate in light of the fact that in many developing countries unqualified and inadequately trained professionals are also designated as "pharmacists". Future policy direction should be in consonance with the concept of seven-star pharmacist, introduced by WHO and adopted by the International Pharmaceutical Federation (FIP) in 2000 in its policy statement on Good Pharmacy Practice that sees the pharmacist as a caregiver, communicator, decision-maker, teacher, life-long learner, leader and manager [11].

6. NGOs, civil society and consumer groups

Civil Society Organizations have a long history of involvement on health and access to essential medicines, consumer protection and promotion of transparency, including many national as well as international groups. In-country CSOs are focused on health in different ways – as service providers, advocates for rights, or providers of care and support for people with specific health problems [12]. While formulating medicines policies, policy-makers need to address various socio-economic, legal, administrative and political factors that act as barriers in the equitable access and rational use of medicines and involve civil society and consumer groups in the policy formulation process. Civil society groups can take social activists and philanthropists from various sections of the society like academia, media, judiciary, health, politics, public service, trade and industry on board & launch a sustained campaign for rational use of quality medicines & make logical interventions through persistent advocacy, persuasive pressure and consistent lobbying in the formulation of robust & comprehensive national pharmaceutical policies, their subsequent implementation in a time-bound manner followed by their continuous monitoring, evaluation and improvement on regular basis. Civil society and consumer associations can act as pressure groups to overcome government inaction and sluggishness in policy implementation by developing adequate political connections with the power centres and utilizing them in the best interests of the policy making and enforcement. By carefully using media, legislature and even judiciary and executive if required in a transparent, legitimate and democratic manner, civil society groups can build pressure upon the governments for timely adoption and implementation of policy provision required to ensure availability and affordability of safe and effective medicines of good quality in sufficient quantities at both private and public sector facilities at all times in a year.

Non-governmental, not-for-profit, self-governed, volunteer-based organizations (NGOs) like *Medicines Sans Frontiers (MSF)*, *Health Action International (HAI), Management Sciences for Health (MSH)* [13] have been doing a commendable job in partnering with governments, civil society, private sector and health care workers to build resilient and sustainable health systems [14]. Their humanitarian missions are saving lives and improving the health of the world's poorest and most vulnerable people by providing medical assistance to people affected by conflict, epidemics, disasters, or exclusion from healthcare. Their role in pharmaceutical policy development remains crucial owing to the fact that their philanthropic activities are driven by the humanitarian spirit of social service and not by any business or profit motives.

In 1999, in the wake of Doctors Without Borders aka Médecins Sans Frontières (MSF) [15] being awarded the Nobel Peace Prize, MSF launched the Campaign for Access to Essential Medicines, since renamed the Access Campaign. Its purpose has been to push for access to, and the development of life-saving and life prolonging medicines, diagnostic tests and vaccines for patients in MSF programmes and beyond.

Similarly in India a NGO named *Jan Swasthya Abhiyan* (JSA) [16] formed in 2001 is constituted of 21 national networks and organizations and state level JSA platforms. Network partners of the JSA include a range of organizations, including NGOs working in the area of health, feminist organizations, people's science organizations, service delivery networks and trade unions. At present it is the major national platform that co-ordinates activities and actions on health and health care across the country. Based on their field experiences, such NGOs can provide significant inputs on how to enhance access to medicines, how to promote their rational use among patients, how to achieve universal health coverage and how to strike a balance between various trade-offs while achieving these goals.

7. Pharmaceutical traders

Pharmaceutical traders including super-stockists, stockists, career and forwarding agents, wholesalers, retailers and medical representatives comprise a crucial link between pharmaceutical industry and the prescribers. They have a big stake in promoting branded medicines due to their business interests and have a very significant potential to circumvent prescribing practices towards that direction. In fact it has been observed that pharmaceutical traders pose hurdles in the implementation of generic drug policies and sometimes even resort to protests and agitation to protect their business interests owing to the fact that generics are a lot cheaper than branded medicines and therefore have little scope for the similar pharmaceutical promotion and marketing practices as are prevalent for the branded medicines. Most of such promotion practices are unethical and several countries like India had to devise rules for curbing such practices that lead to distribution of exorbitant gifts and incentives among physicians that are quite often disproportionate and unjustified [17].

In the year 2009, Medical Council of India (MCI) amended "Indian Medical Council (Professional Conduct, Etiquette and Ethics) Regulation 2002" [18] and brought out the code of conduct for doctors and professional associations of doctors in their relationship with pharmaceutical and allied health sector industry that prohibits them from accepting any gifts, travel facility or hospitality, from any pharmaceutical company or the health care industry. However, even as the Government of India is still debating a code with the drug industry to curb unethical practices, big houses worldwide have started disclosing payments made to physicians, including dollars spent on consulting gigs, clinical trials and even meals. Even though the intention behind framing the code of conduct appears good, the greater issue is the enforcement of these guidelines that seems to be an uphill task. Until and unless MCI or other enforcing body is given enough teeth to enforce these codes, introspection and self-regulation by the doctors remain the only way to curb the ever-rising unethical practices in the health care sector. The proposed self-regulatory code of pharmaceutical companies lacks teeth and has several loopholes since it is not legally binding on companies [19]. Recently in the Supreme Court of India it was revealed by the Federation of Medical and Sales Representatives Association of India, while citing a report by Central Board of Direct Taxes (CBDT), that, "Over Rs 1,000 crore freebies have been given by Dolo

company for the 650 mg Paracetamol formulation and that the doctors were prescribing an irrational dose combination [Ref: Business Today dt. August 19, 2022].

Given such a dismal scenario vis-à-vis ethical pharmaceutical marketing and promotion practices being followed by pharmaceutical companies and traders particularly in developing countries that seriously impairs the implementation of generic drug policies and impedes the progress towards universal health coverage, it becomes essential to undertake sustained negotiations with not only the representatives of pharmaceutical industry but those of the pharmaceutical traders as well so that their genuine grievances, if any are addressed well in time and they are left with no reason to sabotage policy implementation at a later stage. Their involvement and integration with the pharmaceutical policy development process will go a long way in smooth and hassle-free promulgation and execution of the policy provisions and will minimize any chances of obstruction and hindrances in the policy implementation.

8. Health insurance providers

Evidence produced by Sommers et al. [20] on the effects of health insurance on health care and health outcomes in US for the period between 2007 and 2017 revealed that coverage expansions significantly increase patients' access to care and use of preventive care, primary care, chronic illness treatment, medications, and surgery and these increases appear to produce significant, multifaceted, and nuanced benefits to health. They further concluded that some benefits may manifest in earlier detection of disease, some in better medication adherence and management of chronic conditions, and some in the psychological well-being born of knowing one can afford care when one gets sick [20]. This signifies the role and importance of health insurance providers as stakeholders in pharmaceutical policy development.

However, assessing the impact of insurance coverage on health is complex since health effects may take a long time to appear, can vary according to insurance benefit design, and are often clouded by confounding factors, since insurance changes usually correlate with other circumstances that also affect health care use and outcomes [20]. A central aspiration of Universal Health Coverage (UHC) is to protect households from catastrophic health expenditures [21]. UHC aims to provide financial risk protection by increasing prepaid coverage, whether from the fiscal or from health insurance funds, thus decreasing reliance on out-of-pocket expenditure [22]. Governments and national health systems must provide adequate financing to ensure the inclusion of essential medicines in benefit packages provided by the public sector and all health insurance schemes [23].

The path to universal coverage involves important policy choices and inevitable trade-offs. The way pooled funds – which can come from a variety of sources, such as general government budgets, compulsory insurance contributions (payroll taxes), and household and/or employer prepayments for voluntary health insurance - are organized, used and allocated, influences greatly the direction and progress of reforms towards universal coverage [22]. Pooled funds can be used to extend coverage to those individuals who previously were not covered, to services that previously were not covered or to reduce the direct payments needed for each service. These dimensions of coverage reflect a set of policy choices about benefits and their rationing that are among the critical decisions facing countries in their reform of health financing systems towards universal coverage. Choices need to be made about proceeding along each of the three dimensions, in many combinations, in a way that best fits their objectives as

well as the financial, organizational and political contexts [22]. It is here that the health insurance providers as stakeholders can help in making choices during the process of pharmaceutical policy development regarding the best trade-offs that can be made in a given country situation identifying the most needed insurance services, vulnerable populations and cost-sharing packages that are most suitable in the local context.

9. Academia and professional associations

Primary role of the academia and professional associations is to generate evidence through systematic and scientific research that could eventually take shape in the form of a policy document which in turn could be implemented on ground and brought into actual practice. At a later stage they could also research into the effectiveness and outcome of various policy measures and generate evidence for the improvement and modification of policy provisions in the best interest of patients. Thus, continuous monitoring and evaluation of accepted policies could be efficiently achieved leading to constant refining and improvement of the policies at the end of each cycle.

Academia could also conduct research into the actual needs, demands and aspirations of the patients that in turn would translate into policy framework and thus generate need-based policies. Such a bottom-up approach in policy-making could maximize the outcome and minimize the failure rate of government policies and enhance their acceptability among common masses. Academia serves as an important human resource for the governments and drug regulators to bank upon for the expert advice and guidance not only during policy formulation but during policy implementation and evaluation as well. Their constant involvement could lay a roadmap for effective enforcement of policy provisions and help in raising sufficient resources for health, removing financial risks and barriers to access and promoting efficiency and eliminating waste thus clearing the pathway towards Universal Health Coverage.

Professional Societies, Bodies and Associations of experts in the medical field evolve guidelines for the management of various diseases and disorders making use of best practices around the world and making suggestions for the first, second and third choice of pharmacotherapies for the benefit of the patients. These guidance documents could serve as an important resource in arriving at Standard Treatment Guidelines for various diseases and thereby help in devising essential medicines lists and guide Drugs and Therapeutics Committees in their decision-making vis-à-vis selection, quantification and procurement of drugs in hospitals. Therefore, the expert opinion of academia and professional associations could lend a sound scientific foundation to any policy formulation process which makes them important stakeholders in the pharmaceutical policy development.

10. Patients

Last but not the least most important stakeholders of pharmaceutical policy development are the patients since they are at the centre of attention of all other stakeholders mentioned above. They are the end-users of medicines manufactured by pharmaceutical companies, licensed, approved and regulated by governments, marketed, supplied and sold by pharmaceutical traders, prescribed by doctors and dispensed by the pharmacists, thereby making them the fulcrum that bears all the load of efforts and activities of others in the chain. Success or failure of any policy

framework rests upon the relief or hazard that it brings to the patients and provides some succor to them in alleviating their sufferings from the disease. Health indicators, patient satisfaction and overall health of a society can be the outcome measures to judge the success and effectiveness of any newly developed policy framework. Therefore, during the course of pharmaceutical policy formulation needs, demands and aspirations of patients need to be given due consideration in order to make the policy patient-driven and outcome-oriented one. Focus of the policy making has to shift ostensibly from products to patients, from patent protection to patient protection, from industry orientation to public health orientation, from club good to public good, from corporate-driven to consumer-driven framework. That alone can help in making quick progress towards achieving universal health coverage and securing the health and well-being of patients through social solidarity, social security and social justice, for any society that claims to be civilized, just and humane must be able to provide basic health access to its citizens irrespective of their paying capacity.

As we know now, health is not just about diagnosing ailments, hospitals and social services; it is an issue of social justice. Getting good health care is not a privilege; it is considered a fundamental right. Access to essential medicines has been viewed as an integral component of the right to health, which is a basic human right. Ensuring equitable access to quality pharmaceuticals is thus a key development challenge and an essential component of health system strengthening and primary health care reform programmes throughout the world. WHO in its Preamble [24] states, "The enjoyment of the highest attainable standard of health is one of the fundamental Rights of every human being without distinction of race, religion, political belief, economic or social condition [24]."

Article 12 of the 1966 International Covenant on Economic Social and Cultural Rights (OHCHR) [25] recognizes the right of everyone to "the enjoyment of the highest attainable standard of physical and mental health" including through a health-care system that is "economically accessible to all" and details the steps that states should take to achieve this. In consonance with this recognition, providing access to affordable essential medicines in developing countries has been listed as one of the Millennium Development Goals (UNMDG) [26] outlined by United Nations Organization i.e. MDG 8E (MDG, 2008), Target 17, Indict.46. The Millennium Development Goals whose deadline expired in 2015 were followed by the Sustainable Development Goals (UNSDG) [27] with an extended deadline of 2030 that also contain a commitment to "provide access to affordable essential medicines and vaccines, in accordance with the Doha Declaration on the TRIPS Agreement and Public Health". The new 2030 agenda, summarized in the Sustainable Development Goals (SDGs), sets a clear path for future action by placing equity and universal health coverage on centre stage. The health goal, SDG 3 - 'Ensure healthy lives and promote well-being for all at all ages' – underscores the importance of access to medical products and that of the Universal Health Coverage (UHC). UHC is the aspiration that all people obtain the health services they need without suffering financial hardships paying for them.

Coulter [28] has suggested that the twenty-first century health service user is at once 'a decision-maker, a care manager, a co-producer of health, an evaluator, a potential change agent, a taxpayer and an active citizen whose voice must be heard by decision-makers'. In view of all these facts due recognition needs to be accorded to the right to health and the right to equitable access to medicines of patients in any pharmaceutical policy development process and adequate policy provisions need to be incorporated to ensure these rights. Policy-makers need to address both the social determinants of

health, including poverty, and the social determinants of equity, including racism, if they seek to improve health outcomes and eliminate health disparities through their policies. Achieving health equity requires valuing everyone equally with focused and ongoing societal efforts to address avoidable inequalities, historical and contemporary injustices, and the elimination of health and health care disparities [29]. Without the due recognition of these rights of patients any policy development process will be incomplete and inadequate and will not be result-oriented so far as patient satisfaction and well-being is concerned. In fact all drug policy provisions must have the patient as their main focus of attention while being drafted and finalized and the policy planning must be directed at giving maximum relief and benefit to the patients rather than the pharmaceutical industry or the traders.

11. Engagement of stakeholders for pharmaceutical policy development

It is a common practice that governments after drafting policy documents put them in public domain either through print media or through their official websites inviting feedback and suggestions from common masses for their improvement that evokes and yields a few responses from the concerned citizens. However sufficient feedback is not received quite often reducing this whole exercise merely to a formality that hardly bears any tangible results. There is no systematic and organized engagement of various stakeholders mentioned above in some structured manner as a result of which policy document lacks in amalgamation of divergent viewpoints and cross-sectional opinions. In the fitness of things, important stakeholders mentioned above rather need to be consulted and engaged in a very sustained and systematic manner arranging their regular review meetings in clusters and allowing intense brainstorming and refining of ideas. Roberts [30] in his commentary on "Making drug policy together" has argued that stakeholder consultation is intended to inform policy by helping to provide the evidence-base for policy development on one hand and on the other, it provides an opportunity for representation of the views and experiences of a range of individuals and organizations who are interested in and/or affected by drug policy. He further argues that the use of various forms of evidence (for example, statistical data and service user narratives) is critical for meaningful stakeholder engagement and public participation in drug policy, as well as effective policy design and implementation [30].

Stakeholder engagement could be achieved by following means:

1. Constitution of expert committees for policy planning, formulation, implementation, monitoring, evaluation and improvisation.

2. Holding workshops, seminars and symposia in academic institutions for creation of awareness regarding the issues involved and incubation of ideas for policy development.

3. Convening a series of round table meetings of various groups of stakeholders and subject experts in clusters for evolving policy provisions in tune with globally accepted, well established norms and standards.

4. Compiling and consolidating written feedback and suggestions received from common masses, concerned citizens and professional bodies and incorporating valid and relevant suggestions into the final draft.

5. Giving wide publicity to the final draft through print and electronic media by holding discussions on TV and Radio channels and generating further feedback for improvement of the draft policy before its finalization.

Only such a peer review process could lead to development of fool-proof, comprehensive, effective, inclusive, outcome-oriented, coherent, acceptable and well considered policy documents that shall in the long run prove to be successful in achieving the desired health-related goals and objectives. Broadly defined, a stakeholder is a person, group, or organization involved in or affected by a course of action. As per Lemke and Harris-Wai [31] stakeholder engagement refers to the process by which an organization involves people who may be affected by the decisions it makes or who can influence the implementation of decisions. Stakeholders may support or oppose decisions and may be influential in the organization or within the community in which they operate. Stakeholder engagement identifies areas of agreement as well as disagreement and provides an opportunity to understand more fully what might be driving key stakeholder differences. Stakeholder input may also help articulate the values of the broader community affected and align policy recommendations with these expectations [31].

Several different models describe a type of continuum, or different levels, of stakeholder involvement in decision making [32]. For example, the International Association of Public Participation's spectrum of participation defines five broad levels of increasing involvement in the engagement process: (i) inform (e.g., fact sheets, websites, open houses), (ii) consult (e.g., public comment, focus groups, surveys, public meetings), (iii) involve (e.g., workshops, deliberative polling), (iv) collaborate (e.g., citizen advisory committees, consensus building, participatory decision making), and (v) empower (e.g., citizen juries, delegated decisions) [33]. Although there is no perfect, one-size-fits-all model for developing policies or guidelines, defining stakeholder roles in any or all stages of genomics policy making is important to better evaluate and understand the policy-making process. A number of frameworks have been developed in various disciplines to assist policy makers in planning for policy development and analysis, and some include a specific component addressing key stakeholder consultation [34, 35].

Conklin et al. [36] have concluded from the results of a systematic scoping review that there is a need to build research capacity through incentives for more robust evaluations of public involvement in healthcare policy and to synthesize a better evidence base that consistently takes a common approach. In so doing, a greater step can be made towards a stronger evidence base for whether public involvement improves processes and/or outcomes of decision making and policy. Such evidence is a minimum requirement for comparatively assessing which areas of health-care policy are the most amenable to the use of public participation and then within a given area, what type of public involvement makes a difference in what context(s) [36]. In 2015 WHO published guidelines for developing country pharmaceutical pricing policies in which it was reiterated that "in establishing the legislative/administrative framework, countries should clearly define the roles and responsibilities of the decision-makers and other stakeholders, and the process of decision-making and the countries should ensure that health technology assessment processes are transparent and the assessment reports and decisions should be made publicly available and effectively disseminated to all stakeholders [37].

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Chapter 3

Embracing the Changing Needs for Pharmacovigilance in Africa

Babafunso Aderemi Adenuga

Abstract

Growing burden of communicable and non-communicable diseases in sub-Saharan Africa has necessitated the need for increased medicine use among the African population. Owing to the limited manufacturing capacity of medicines in the sub-continent, it became imperative for governments and Central Medical Stores to source medicines from countries such as India, Bangladesh and China. Such procurements were due to the affordability of generic products manufactured by manufacturers in these countries compared to innovator s, which might come at exorbitant prices and costs that might be prohibitive for most developing countries such as the ones in sub-Saharan Africa. Ascertaining the quality and efficacy of these products are always reliant on the judgment of national regulatory authorities (NRA), which might be ill equipped in most instances; human capacity both in knowledge and number are some of the banes of such NRAs. Aforesaid, pharmacovigilance does not take the front seat in most discussions rather the burden of diseases, thus the emphasis on medicines availability. Different researchers have highlighted the link between medicines/drugs availability and the need for pharmacovigilance among healthcare workers, policy makers and patients. Such approach will tend to limit the procurement of medicines that are substandard, falsified or fake, with the aim of protecting public health.

Keywords: sub-Saharan Africa, pharmacovigilance, students

1. Introduction

Pharmacovigilance is a necessity in any healthcare setting [1]. Adverse drugs reactions (ADR) reporting, a major part of pharmacovigilance, is either not reported or under-reported in different settings all over the world [2]. Number of ADR reports received by a national pharmacovigilance centre reflects how effective the pharmacovigilance systems are, within the country [3]; it is the role of regulatory agencies which are either part of Ministries of Health or parastatals within such ministries to ensure the quality, safety and efficacy of medicines that are approved by National Regulatory Authorities (NRA), thus, protecting the health of the population. Development of effective systems to mitigate gaps due to low level of pharmacovigilance in the healthcare system so as to enhance ADR reporting by both healthcare workers and patients is important [4].

It should be emphasized that policy development and enforcement of implementation of such policies are important and integral role of Ministry of Health through their

departments such as the Namibia Medicines Regulatory Council (NMRC), South Africa Health Products Regulatory Agency, Medicines Control Authority of Zimbabwe, etc.

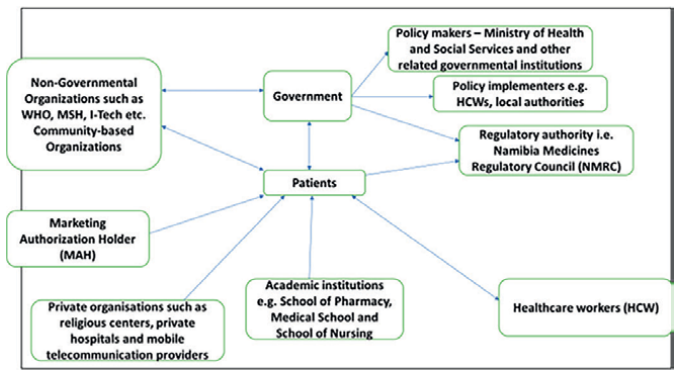
Using Namibia as an example, the number of ADR reports received by the Therapeutic Information and Pharmacovigilance Centre (TIPC) is relatively low in comparison to the population [5]. This is not in line with the stated number of reports that should be submitted to WHO Upsala Monitoring Centre (WHO-UMC), i.e. 200 reports per 1,000,000 population; with an assumption that a country with a population similar to Namibia should be reporting at least 400 ADRs per year. Below is a figure showing the number of ADR reports submitted to NMRC between 2009 and 2019.

According to Kiguba et al. [6], health systems in low- and middle-income countries (LMICs) are fragile, this is reflected in the capacity of pharmacovigilance structures available within the health systems. As highlighted earlier, the number of ADR reports submitted to pharmacovigilance centres is an indication of the strength of that system. Some of the factors associated with observed challenges facing pharmacovigilance centres and invariably, the structures, which include,

1. Integration of pharmacovigilance activities into mainstream healthcare system
2. Unreliable pharmacovigilance systems
3. Capacity and capability of pharmacovigilance personnel
4. Undefined relationship between regulatory authority and marketing authorisation holders
5. Reporting tools or modalities that are outdated
6. Awareness among healthcare workers and patients
7. Unavailability of drug utilization data

1.1 Linking the unlinked

According to Adenuga et al. [5], it is imperative to develop effective links between stakeholders within the healthcare system and outside it so as to achieve the goal of effective pharmacovigilance. Below is a conceptual framework developed by the authors. The central theme is focused on patients. Effective pharmacovigilance of medicines is part of the Sustainable Development Goals (SDGs) [7].



(Adapted from Adenuga et al. [5]. Conceptual framework for effective stakeholder engagement for pharmacovigilance in a resource limited setting)

Funding of health programs has been a bane of developing the healthcare system in some developing countries [8, 9], with most funding coming from donor organisations such as United States Agency for International Development (USAID), FHI 360, Bill and Melinda Gates Foundation and other similar organizations [10, 11]. An example is the establishment of the Pharmacovigilance Centre in Namibia through funding from USAID.

Marketing Authorisation Holders (MAH) of registered medicines can be engaged in patient management with regard to pharmacovigilance, especially, with respect to the applicants who register generic products, might assist in better pharmacovigilance of such medicines or products.

2. Making a case for improved pharmacovigilance

Pharmacovigilance (PV), the practice of the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem, has been promoted over the last two decades in Low- and Medium-Income Countries (LMIC). Nonetheless, the systems and coordinated efforts to support the reporting of Adverse Drug Reactions (ADRs) remain suboptimal in these settings [12]. The Therapeutic Information and Pharmacovigilance Centre (TIPC), a unit of the Ministry of Health and Social Services, Namibia, is a case in point. The quantitative and qualitative impact of such centres in SSA, on informing policy change on drug choice, safety and effectiveness of medicines Namibia remains underutilized.

Healthcare workers in both public and private healthcare facilities in Namibia are believed to under-report ADRs; this might be partly due to a poor acceptance and implementation of pharmacovigilance systems at health facility level [13, 14]. In most LMICs such as Ethiopia, among the factors that promote under-reporting of ADRs, are lack of awareness of ADRs Monitoring Centres (AMC) and pharmacovigilance program in the settings, complacency, lack of training to identify ADRs etc. [15, 16]. In addition, about half of the health workers do not know how to report ADRs and/or are not aware of the existence of a formal ADR reporting schemes.

2.1 Improving adverse drug reactions reporting in resource limited settings

Healthcare workers are vital to effective reporting adverse events within healthcare systems; however, the place of patients should not be under-emphasized. In a country like Namibia where most or all of the reports received by the TIPC come from healthcare workers, such system does not have the political strength to empower patients to report whatever they experience after they have left healthcare facilities and started taking medicines prescribed. It is evident that the reports submitted to TIPC will be limited, thus, it is necessary for the system to create awareness by promoting pharmacovigilance among the populace.

Another vital area that should be looked at it, is the mode of reporting. In the **Figure 1** above, it reveals the average number of reports submitted to TIPC over a period of 10 years. It should be highlighted that the reports were made using the Yellow Form – paper-based reporting modality, this has its limitations, especially in

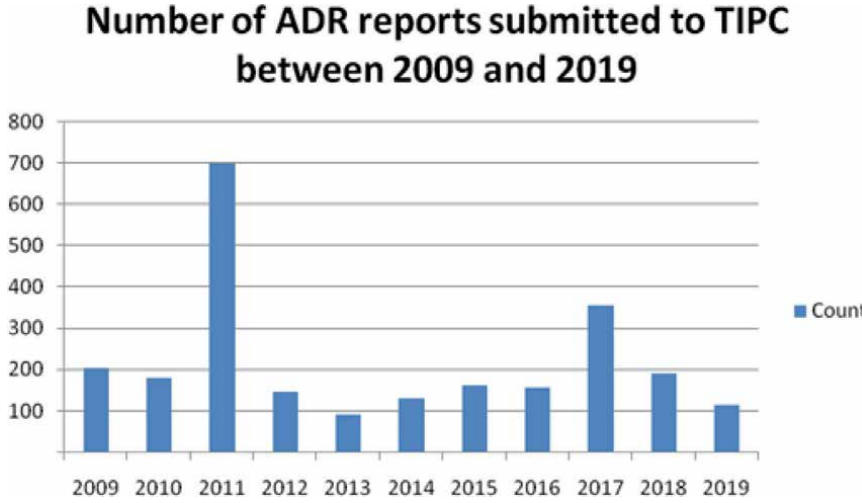


Figure 1.
Number of reports submitted to TIPC per year, between 2009 and 2019 (adapted from [5]—Developing an electronic mobile reporting modality for pharmacovigilance in Namibia).

an era of advanced electronic communication, Adenuga et al. [5], commented on the need to develop a mobile electronic platform for reporting of ADRs which will be accessible to both healthcare workers and the entire populace. An engaging session that will not only focus on the healthcare professionals can assist in mitigating the low number of ADR reports in a LMIC such as Namibia.

Stakeholders such as policy makers and healthcare workers at different levels of the health system has to be aware of the possible impact of adverse events such as ADRs, medication errors, etc. on individual patient and the health system as a whole, thus the need to develop policies, guidelines and advocacy programs geared towards better patient management, which might include proper record keeping at every level of the healthcare delivery system. Economic consequences of a huge burden of ADRs can undermine the provision of quality healthcare services. This calls for both social inclusion and intersectoral engagements of entities such as Non-Governmental Organisations (NGOs) and Community-Based Organisations (CBOs), which might have closer relationships with people at the grassroots (patients being the focus of such activities), thus, might be able to pass across the "gospel effective medicine stewardship".

Primary Health Care (PHC) facilities such as clinics and health centres, are the first contact of patients with the health system, these should be utilized in maximizing the reach of pharmacovigilance campaigns. Educating healthcare workers at PHC level on the need for effective pharmacovigilance will go a long way in mitigating the impact of adverse events on patients, health system and the country as a whole. It should be highlighted the adverse events have both debilitating and mortifying effects on individuals and can negatively impact the growth of a country if conscious efforts are not taken to put their development in check.

Engaging healthcare workers in the private settings on the need to know and realize the necessity of reporting suspected adverse events will reveal the inclusiveness of the endeavour; with pharmacovigilance being a collaborative activity, it is essential that every stakeholder should be involved. The need to engage every stakeholder including patients cannot be over-emphasized.

For this to be achieved, political will and effective stakeholder engagements will be vital. Adenuga et al. [17], highlighted how this can be achieved.

Some strategies that can be used to social inclusiveness and effective stakeholder engagements are explained below.

2.2 Introducing pharmacovigilance into the curriculum of healthcare workers

A shift in the training paradigm of healthcare workers through the introduction pharmacovigilance into both pre-registration and registered educational systems might improve pharmacovigilance and subsequently reports being generated by these healthcare workers.

Incentives such Continuing Professional Development (CPD) points, can serve as an encouragement for some healthcare workers. This was highlighted by respondents in study carried out by Adenuga et al. [14].

2.3 Social engagements and needs assessment

Tailoring interventions to the peculiarity of communities requires social engagement and needs assessment. In settings with low pharmacovigilance knowledge and practice among healthcare as seen in many sub-Saharan African countries [18], it is necessary to develop interventions that are locally feasible and acceptable so as to achieve the goals of pharmacovigilance. Creation of awareness among patients/general population (primary stakeholder), healthcare workers at different levels of the health system (students and workers), policymakers (government, non-governmental organisations (NGOs), community-based organisations (CBOs) and private sector (health- and non-health related)) is important. Such awareness programs have to be suited to the group in question, so as to be able to produce the desired results.

Pharmacovigilance Centres can carry out public awareness campaigns for example road-shows or through dedicated activities t cultural events, to highlight the need for pharmacovigilance. Such an initiative will help improve public awareness regarding pharmacovigilance, ADRs and their reporting.

2.4 Policy development and implementation

Development of policies and guidelines by the health policymakers at different levels of the healthcare delivery system, in conjunction with other stakeholders, that will enhance pharmacovigilance. Policies developed should assure healthcare workers there will be no litigation or reprimand for reporting whatever event they picked up or encounter in the course of managing their patients. In other to achieve effectiveness of policies, implementation pathway has to be incorporated into the policies and proper management frameworks should be itemized prior to rollout of the policies.

Effective engagement with stakeholders involved in the development of these policies, implementation and eventual rollout will not be cumbersome if everyone was carried along from the onset and they realize each one of them has a role to play.

2.5 Inclusive pharmacovigilance systems

Social inclusiveness has been highlighted as one on of the ways of engaging the community in pharmacovigilance activities, such inclusiveness should be centred around patients. Enhanced functionality of Therapeutic Committees at the facility

and regional levels in pharmacovigilance activities might assist in the promotion of better patient management and contribute to a reduction in the costs due to ADR. However, patients or their advocates or representatives can be included in Therapeutic Committee meetings, thus, allowing them to see and appreciate what goes into patient management.

Patient reporting platforms, either in an electronic format or paper-based systems, can assist in getting first-hand reports, thus, boosting the number of ADR reports received by Pharmacovigilance Centres. Patient reporting has been identified as one of the avenues that might contribute to more ADR pool within a country in some settings. In this vein, allowing the general population to provide the regulatory authority with reports will be seen as improved awareness and such an initiative will, in the long run reduce ADR burden thus, affording the Ministry of Health better patient management.

Considering widespread use of electronic devices, introduction of a mobile electronic platforms for reporting ADRs, working in conjunction with mobile telephone networks at no cost to reporters might assist in boosting the number of reports received or submitted to pharmacovigilance centres. Paper-based reporting modality cannot be phased in the nearest future, taking into consideration those areas within the country or individuals with no access to electronic devices.

2.6 Inclusion of patient information leaflet (PIL) in every product

Mandatory inclusion of the details of MAH pharmacovigilance person within their organisation (preferably based within every country where their product is marketed) in the PIL accompanying medicines dispensed to patients will assist patients in knowing where to direct their enquiries or reports apart from their National Pharmacovigilance Centres; this can promote ease of reporting by the public/patients. In other for this initiative to be effective, pharmacovigilance centres along with the policymakers at the MoH will have to develop policies or regulations that will strengthen this position.

Since knowledge is vital in pharmacovigilance, inclusion of PIL in medicines packs that are self-administered by patients will help patients gain knowledge of the medicines they are taking and what ADRs to expect.

2.7 Standard operating procedures (SOP) in private practice settings

Pharmacovigilance Centres in conjunction with private healthcare practitioners can develop SOPs that will be kept at facilities. Such SOP will assist healthcare workers in ADR management and reporting, and all employees within the practice should be trained on such. The private practices envisaged should include suppliers of pharmaceuticals (i.e. wholesale distribution outlets, compounding pharmacies) and manufacturers.

2.8 Advocacy and educational interventions

Pharmacovigilance has an impact on the overall health of a population and the cost of healthcare services. In particular, strengthening the health system through incorporation of pharmacovigilance into the curricula of different healthcare cadres training schedules will add value to the academic learning and invariably assist in reducing the cost that might have been incurred due to ADRs. Thus, emphasis should be placed on inculcating good reporting culture by the students, not neglecting continued professional training of healthcare workers within the public and private healthcare settings.

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Different stakeholders that contribute or are involved in healthcare provision and consumption (patients) need to be reached and made aware of the place of pharmacovigilance and the need for ADR reporting in patient management. Enlightening healthcare workers, policymakers and patients is an essential aspect of the promotion of pharmacovigilance; they need to be acquainted with ways of identifying whatever reaction occurs after the use of any clinical intervention such as medicines or unusual laboratory results and realize that such event requires reporting to the TIPC or any reporting centre within their region, will be paramount to optimizing the pharmacovigilance system.

3. Conclusions

We have explored possible ways of improving pharmacovigilance among healthcare workers, patients and other stakeholders within the public and private healthcare setting in SSA. Social inclusiveness and engagement are pivotal in understanding the current state of pharmacovigilance in the region.

Conflict of interest

The author declares no conflict of interest.

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Chapter 4

Approach to Minimize Adverse Drug Reactions in Elderly

Hima Bindu Gujjarlamudi

Abstract

The elderly, above the age of 65, are heterogeneous population with increased morbidity. They are more exposed to medication due to multiple health problems. The natural physiological changes and alterations in homeostatic regulation alter drug response and increase the risk of adverse drug reactions in them. Multi-prescription, polytherapy also increases the incidence of adverse reactions. It is difficult to diagnose adverse reactions in the elderly as they often present with nonspecific symptoms and to differentiate whether they are due to medications or not. Most of the hospital admissions due to adverse reactions are predictable and 50% among them are preventable Type A reactions as most of the errors occur during prescribing or monitoring of drugs. Prescribers should review the medication list regularly and be cautious in prescribing new medicines. Physicians' awareness of the physiology and pharmacology of aging can reduce adverse reactions that help in promoting better health care for older adults.

Keywords: elderly, adverse reactions, polytherapy

1. Introduction

The population of the elderly is increasing worldwide. India is going to be the highest in Asia with people aged 60 years and above. In 2020, there are an estimated 727 million persons aged 65 years or above worldwide. It may be doubled by 2050, nearing to more than 1.5 billion persons. The share of older persons in the global population is expected to increase from 9.3 percent in 2020 to 16.0 percent in 2050 [1]. As age advances, they are more exposed to multiple diseases in addition to the increased incidence of other illnesses such as Alzheimer's disease, Parkinson's disease, vascular dementia, stroke, arthritis, and fractures [2]. So, medications play a crucial role in geriatric health care as they treat chronic diseases, reduce pain, and improve quality of life [3].

The physiological changes that occur with aging alter the pharmacokinetics and pharmacodynamics of drugs, which increases the risk the adverse drug reactions (ADR) and drug interactions (DI). Multi-prescription, polytherapy, and inappropriate medication use also increase the incidence of ADR. A major threat to the health-related quality of life of older adults is ADRs. They can decrease functional status and increase the use of health services and costs, as well as mortality [4]. Hence this

article focuses on the prevalence and risk factors for ADR in older adults and the steps taken to minimize them.

2. Prevalence of ADR in older adults

ADR is defined as "an appreciably harmful or unpleasant reaction resulting from an intervention relating to the use of a medicinal product" [5]. Compared with younger patients, patients aged 65 years or older are seven times more likely to have an ADR requiring hospitalization [6]. ADRs are responsible for 5–28% of acute geriatric hospital admissions, and studies have indicated that more than half of them are preventable with only 19–28% of ADRs causing hospital admission in older patients considered unavoidable [7].

A study done by Harugeri et al. [8] in a hospital setting found that the prevalence of ADR-related hospital admissions was 5.9%, while in another study [9] in India, it was observed to be 6.7%. In-hospital incident ADRs cause a 9% increase in length of stay and a 20% increase in the cost of care encompassing bed consumption, laboratory, and treatment costs [10]. About 20% of ADR-related hospitalizations need blood products to treat gastrointestinal bleeding adding to extra cost on the patient [11].

3. Risk factors for ADR in elderly

Several factors contribute to the higher incidence of ADR. **Table 1** highlights the list of risk factors for ADR in the elderly. Older people experience greater morbidity with a corresponding increase in medication utilization resulting in a higher risk of ADRs [12].

3.1 Physiological changes

The natural physiological changes that occur due to aging and alterations in homeostatic regulation alter drug response and increase the risk of ADR in them. Drug metabolism and clearance change with alterations in pharmacokinetics [13] further increasing the risk of ADRs. The decrease in total body water alters the volume of drug distribution prolonging the half-life of a drug and increasing the risk of toxicity [14, 15].

S.No	Risk factor
1	Physiological changes in elderly
2	Polytherapy
3	Nonadherence
4	Use of PIMs
5	Medication errors
6	Multimorbidity

Table 1.
List of risk factors for ADR.

The filtration capacity of the glomerulus reduces as age advances, which results in the decreased excretion of drugs and an increase in adverse reactions.

3.2 Polytherapy

Multi-prescription, polytherapy also increases the incidence of adverse reactions. It was estimated that more than 60% of the elderly take five or more drugs regularly. The risk of ADRs is increased with the increase in the number of medicines prescribed [16]. This has been estimated at 13% for two drugs, 58% for five drugs, and 82% for seven or more drugs [17].

3.3 Nonadherence

Complex medication regimens related to polypharmacy can lead to nonadherence in older adults [18]. Nonadherence can lead to serious sequelae, including disease progression, treatment failure, hospitalization, and adverse drug events [19].

3.4 Potentially inappropriate medications

The use of potentially inappropriate medications (PIMs) in the elderly has also been described as a potential cause of ADR [20]. PIMs use increases the risk of hospitalization, drug-related problems, and other adverse health outcomes by two to three folds [21]. For example, drug-related problems secondary to the inappropriate use of sedatives and hypnotics among older adults are found highly associated with the risk of falls, delirium, and hallucination [22].

3.5 Medication errors

Errors in medication administration and autonomous modification of medication schedules have also been reported to contribute to ADRs [23]. Another important risk factor for developing ADR is its previous occurrence. Re-exposure to offending drugs due to poor documentation can cause the same ADR.

3.6 Multiple diseases

The risk of ADRs also increases with an increasing number of chronic diseases. When medicine was given to treat one condition, it aggravates the signs or symptoms of another underlying disease. For example, beta-blockers taken for cardiovascular disease worsen asthma symptoms or metoclopramide for gastric dysmotility worsens motor symptoms of Parkinson's disease [24].

4. Common drugs causing ADR in elderly

The majority of ADRs in older people are Type A reactions that is, they are attributable to a predictable known pharmacological effect of a drug. Type A adverse drug reactions are usually avoidable and typically involve commonly prescribed medications [25]. There are many drugs to be avoided or used with great caution in the elderly. The most frequently implicated drug groups causing ADRs in the elderly are antibiotics, cardiovascular drugs, steroids, loop diuretics, hypoglycemic,

S. no	Name of the drug
1	CNS drugs, especially benzodiazepines, anti-psychotics, antidepressants
2	Anti-hypertensive agents
3	Diuretics
4	Anti-arrhythmics: Quinidine, Digoxin
5	Non-steroidal anti-inflammatory drugs—Aspirin
6	Corticosteroids
7	Anti-coagulants—Warfarin
8	Antibiotics
9	Antipsychotics
10	Benzodiazepines

Table 2.
Common drugs causing ADR in older adults.

antipsychotics, and antidepressants (**Table 2**) [26]. A systematic review of nine studies of ADRs as a cause of hospitalization found that 51% of preventable drug-related admissions were associated with antiplatelet agents (16%), diuretics (16%), NSAIDs (11%), or anticoagulants (8%) [27]. A drug combination may sometimes cause synergistic toxicity, which is greater than the sum of the individual toxicities used alone. The risk of the development of NSAID-induced peptic ulcers in the elderly may increase by 10% when used along with corticosteroids [28]. However, concurrent use of corticosteroids and NSAIDs had shown a risk of peptic ulcers, which was 15 times greater than that of non-users of either drug [29].

5. Steps to reduce ADR in older adults

The main factor in reducing ADR is its correct identification. It is difficult to recognize ADR in older people as they often present with nonspecific symptoms such as falls, fatigue, cognitive decline, or constipation. The inability to distinguish drug-induced symptoms from a definitive medical diagnosis often results in the addition of yet another drug to treat the symptoms, which increases drug-drug interactions and ADR, known as "the prescribing cascade" [30]. For example, anti-Parkinsonian drugs are prescribed to treat motor symptoms occurred due to prolonged antipsychotic therapy. The risk of ADR can be reduced by regular monitoring of the patient, prompt identification of symptoms, and the effect of medication on different organs. Hence, both the prescribers and patients play an equal contribution in reducing the risk of ADR in the elderly.

5.1 Role of prescribers

5.1.1 Examine the patient

A systematic approach to the patient will reduce ADR. The patient has to be examined thoroughly in a comprehensive view, not just focusing on symptoms alone.

As symptoms can be adverse reactions to the drugs or due to disease progression, patient's treatment need has to be identified and documented by the diagnosis.

5.1.2 Maintain the record

All drugs used by the patient including non-pharmacological agents such as herbal preparations, supplements, or over-the-counter (OTC) medications are recorded because alternatives or herbals may interact with the present regimen, increasing the risk of adverse reactions. The most commonly used herbals and dietary supplements are glucosamine, extract of gingko biloba, St. John's wort, and ginseng. A study in the United States found that out of 3072 ambulatory elderly patients, 82.5% used at least one supplement and 54.5% used three or more [31]. A record of all medications including herbals and other alternatives should be updated frequently with possible simplest regimens to reduce the duplication, unnecessary medication, and important drug interactions. It also reduces polypharmacy and the underuse of vital drugs.

5.1.3 Benefit-risk assessment

The elderly patient is evaluated for benefits and risks while prescribing the medication. This reduces the use of unnecessary medication or duplication, and polypharmacy and further reduce the cost burden on the patient.

5.1.4 Adjust the dose of the drug

Aging decreases the filtration capacity of the glomerulus because of a decrease in renal size, perfusion, and nephron function [32]. Glomerular filtration rate must be calculated for drugs eliminated through the kidney. The dose of the drug has to be adjusted for renal impairment by using Cockroft and Gault Equation to minimize the risk of ADR.

5.1.5 Inappropriate medications

The use of inappropriate medications is most common in elderly patients. Approximately 50% of the elderly take one or more medications that are not necessary [33]. The Beers criteria are the most commonly used criteria to guide prescribers in preventing ADR [34, 35]. This was recently revised in 2019 by an expert panel sponsored by the American Geriatric Society. Screening Tool of Older Person's Prescriptions (STOPP) is another tool consisting of 65 STOPP criteria to represent common avoidable instances of inappropriate prescriptions [36]. "The Good Palliative–Geriatric Practice algorithm" for discontinuation of drug reduced polytherapy and improved morbidity and mortality in community-dwelling elders and nursing home inpatients [37]. These criteria consist of drugs to be avoided or used with caution in the elderly and reduce inappropriate prescribing and its related ADR. In the elderly, underuse of medicines is also prevalent. Prescribers may underuse the useful drug if the patient is not able to afford the medication. START (screening tool to alert doctors to the right treatment) is a tool designed specifically on the list of evidence-based useful medications but possibly omitted drugs in the elderly [38]. This can be reduced by documenting the patient's condition and prescribing the medication for the current condition.

5.1.6 Start with a low dose

Aging alters the pharmacodynamic responses. So, the elderly are more sensitive to the effects of drugs than young adults even with standard doses. Drugs such as morphine and neuroleptics cause more confusion and warfarin increases the anticoagulation effect with a regular therapeutic dose. This can be minimized by starting with the lowest possible dose and gradually titrating the dose depending on the response by carefully monitoring the patient.

5.1.7 Drug frequency and dosing

The time of drug administration also plays a role in the development of ADRs. Chronotherapy is the delivery of a drug following biorhythm that prevents an overdosing of any class of drug [39]. Patients with osteoarthritis have less pain in the morning and more at night. NSAIDs reduce pain when given at least 4–6 hrs before the pain reaches its peak. So, it is given around noon or midafternoon [40]. The incidence of ADR can be reduced by administering the right drug at the right time.

5.1.8 Drug interactions (DI)

Drug-drug, drug-disease, and drug-food interactions should be considered while prescribing to the elderly. Co-morbidities and polytherapy in the elderly increase the risk of DI. The prevalence rate of DI-induced ADR-related hospitalizations was 22.2% and 8.9% for hospital admission and hospital visits, respectively [41]. The most important DI occurs with drugs that have serious toxicity and a low therapeutic index. Bisphosphonates are often co-prescribed with calcium supplements in the treatment of osteoporosis. Calcium binds to the bisphosphonates and reduces its absorption with the possibility of therapeutic failure [42]. This may be avoided by allowing a sufficiently long dosage interval; the possible approach is to give bisphosphonates for 2 weeks and calcium supplements for 10 weeks [43].

The risk of potential drug interaction increases from 39% to 100% when patients are on more than six medications compared to when they are on 2–3 medications [44]. Most of the DI can be reduced by choosing alternative medications that are not associated with DI. For instance, pantoprazole is given to patients on clopidogrel in place of omeprazole to avoid interaction between omeprazole and clopidogrel.

The risk of drug-disease interaction is also important as the elderly population suffers from more than one condition. The most common interactions were aspirin and peptic ulcer disease; calcium channel blockers and heart failure and beta-blockers and diabetes [45].

These interactions are of utmost importance as they decrease the efficacy of the drug or may increase the toxicity of a drug. Hence, prescribers must have knowledge on the pharmacology of drugs and their interactions to reduce DI-related ADR.

5.1.9 Economical alternative

Strict adherence to the medication is very important to reduce the progression of the disease, treatment failure, and further adverse effects. An increase in the cost of medications reduces adherence to the treatment. The pill burden can be reduced by using medications that can control two or three conditions and by choosing economical alternative drugs [46].

5.1.10 Patient education

Patients and their families should be educated about the effects of polytherapy and can stop the unnecessary medication if there is no benefit. Counseling is given on the probable adverse effects of the drugs, adherence to the therapy, and sudden stoppage of treatment. The plan of treatment, its effects, and follow-up visits should be clearly discussed with the patient and their families.

5.2 Role of patients/caregivers

Elderly patients or their caregivers play an equal role in reducing the incidence of ADR. In a study of 30,000 Medicare enrollees aged over 65 years followed for a 12-month period, 99 adverse drug events (23.5% of all adverse drug events) and 30 potential adverse drug events (13.6% of potential adverse drug events) were attributed to patient error [23]. Errors in medication administration, adherence to the treatment regimen, and modification of medication schedules are commonly encountered patient errors.

5.2.1 Information about medications

The elderly patients and their informal carers should obtain clear information about the effects of drugs, the timing of administration, and diet restrictions. They must have minimum knowledge of common side effects of their drugs and drug interactions so that they can inform their physician immediately when they occur for necessary action.

5.2.2 Improving the compliance

Poor adherence to the prescribed regimen is most common in the elderly, which compromises the efficacy of the drug. Dementia, decreased vision, financial constraints, and too frequent administration of medication further decrease compliance. Some patients decrease the dose of the drug or may even stop the drug because of undesirable effects without informing the physician. Strict adherence to treatment should be enhanced by using daily or weekly pill boxes, setting alarm clocks, and daily reminders.

5.2.3 Use of over-the-counter drugs (OTC)

The patient has to inform all the drugs they are using, including OTC, herbals, or other supplements, which helps the physician in identifying ADRs and DI. In a telephonic survey in North America, 34% cohort was taking at least one unintentional drug and 72% of them reported that they did not inform their clinician about this [47]. Herbal medications interact with the current regimen resulting in adverse effects. Severe bleeding with warfarin and ginkgo, garlic; exacerbation of extrapyramidal effects with neuroleptic drugs, and betel nut; potentiation of oral and topical corticosteroids by licorice are some of the examples [48].

5.2.4 Maintain the record of medications

A list of medicines should be updated regularly and brought to the clinician during the visits. All the duplicated medicines and unnecessary medications should be deleted.

6. Conclusion

Prescribing drugs in the elderly is a serious challenge as there is an increased possibility of drug interactions and ADR. It is difficult to balance beneficial therapy and inappropriate medication. Prescribers need to know what other prescriptions the patient is taking, including herbs and supplements, and the drug regimen is evaluated periodically to reduce polypharmacy. ADR is considered in every differential diagnosis. Good communication should be maintained among health care providers, patients, and caregivers. Physicians' awareness of the physiology and pharmacology of aging can reduce adverse reactions, which helps in promoting better health care for older adults.

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Chapter 5

Pharmacovigilance of Biological Drugs

Simona Guerzoni, Flavia Lo Castro, Carlo Baraldi, Giuliana Colella and Luca Pani

Abstract

The use of biological drugs has significantly increased over the past decades and has allowed for the treatment of many life-threatening and chronic diseases. The patent expiration of biological innovative medicines enables copies of these drugs called biosimilars. The availability of biosimilars enhances competition, with the potential to improve patient access to biological medications and contribute to the financial sustainability of the healthcare systems. Unlike equivalent drugs, biosimilars are not identical but similar to their innovator products because of the differences in the manufacturing process, which is a biological process. However, they are considered comparable to their originators in safety, quality characteristics, biological activity, and efficacy. The regulatory procedures used for generic drugs cannot be applied for biosimilars, so they are subjected to rigorous characterization as well as comparative clinical studies. Since they are highly complex molecules produced from living cells, even small change in the production process can have major implications on their safety and effectiveness profile, causing a potential risk of immune-based adverse reactions. For all these reasons, for biological drugs, a robust long-term pharmacovigilance system is necessary. It is desirable that in the future, there are further guidance and resolution of the ongoing discussions on biosimilar labeling, naming, pharmacovigilance and interchangeability/substitution, to ensure the appropriate use of these drugs in clinical practice.

Keywords: biologic, biosimilar, pharmacovigilance, regulation, interchangeability

1. Introduction

Biological drugs have overturned the classic concept of medicine and pharmacology. They are now one of the cornerstones of modern medicine and the so-called "targeted therapy" or "personalized therapy," which acts specifically on a given target. Biological drugs are henceforth referred to as "biologics" in this work. Biologics include various products, such as hormones and enzymes, blood products, and immunological drugs (serums, vaccines, immunoglobulins, allergens, and monoclonal antibodies) [1].

These therapies have drastically improved the prognosis of several severe and life-threatening diseases, such as cancer, diabetes, and autoimmune diseases (e.g., rheumatoid arthritis, Crohn's disease, multiple sclerosis, and severe psoriasis) [2, 3].

Biologics are very different from "conventional drugs" in origin, structural complexity and variability, manufacturing process, side effects (immunogenicity), and regulatory aspects. This makes the pharmacovigilance of biologics particularly complex.

It should also be emphasized that a huge commitment of resources burdens therapies derived from biotechnologies and this, as repeatedly stressed by the various regulatory agencies, poses a significant problem in terms of economic sustainability at the global level. "Biosimilars", which are similar to original biologics that are no longer subject to patent protection, and can be marketed at lower prices than actual products, fit into this context, further complicating the already tricky pharmacovigilance for biologics.

2. Biological drugs: critical aspects

2.1 Definition

According to the definition of biologics provided by the European Medicines Agency (EMA), "a biological drug is one that contains one or more active substances derived from a biological source. Biologics are larger and more complex molecules than non-biologic ones. Only living organisms can reproduce this complexity" [4]. Most biologics in current clinical use are proteins. They can differ in size and structural complexity, from simple proteins, such as insulin or growth hormone, to more complex ones, such as coagulation factors or monoclonal antibodies [2, 3, 5].

Biologics, including "biotech" drugs, that is, those produced by biotechnological methods (including recombinant DNA technologies, controlled expression of genes encoding biologically active proteins in prokaryotes or eukaryotes, hybridoma-based methods, and monoclonal antibodies), consist of active substances obtained from living cells or organisms [6]. Biologics production is a complex process involving gene manipulation, fermentation, and purification steps. It requires a very high level of technical expertise, sensitivity, and control to ensure its safety and efficacy. Generally, the first step is modifying a cell or microorganism, considered to be the host, to introduce a genetic sequence coding the protein to be produced. Then the host is conserved, and a master cell bank is produced from a seed lot. They are picked up, cluttered, and grown in a bioreactor or fermenter. Finally, it is collected to purify the protein, which will be then stabilized and formulated for therapeutic use.

Any changes in these processes, such as differences in temperature or pH, or cell culture conditions, could cause a significant modification in the final product in terms of efficacy or safety [7]. Moreover, due to post-translational changes, such as glycosylation, oxidation, and deamination, the final product may differ slightly from batch-to-batch and even within the same batch, they may have an impact on the mechanism of action of the molecule.

Since an ineluctable and unpredictable variability characterizes all living organisms, even if minimal, what is obtained from a biotechnological process will have an "intrinsic degree of minimal variability." Therefore, unlike generics where an exact copy can be made, in the case of biologic production, it is said that "the process defines the product" [8].

2.2 Immunogenicity

Another aspect that differentiates biologics from "conventional drugs" is their immunogenic potential, that is, their ability to induce an immune response in the

	Generics	**Biosimilars**
Synthesis	Chemical	Biological
Structure	Structurally simple small molecules	Structurally complex large molecules
Risk of immunogenicity	Low	High
Comparative studies	No needed	Needed
Interchangeability	Yes	EMA does not specify; for FDA it's possible but after studies
Substitutability	Yes	EMA does not specify; for FDA, it is possible but after studies
Nomenclature	INN	No specific for EMA; specific for FDA
ADR'S report form	INN and manufacturer	Name and batch number
Registration dossier	Simple	Complete
Risk management plan	No needed	Needed
Additional monitoring	No needed	Needed

Table 1.
Differences between generics and biosimilars.

body (**Table 1**). Immunogenicity can lead to the development of antidrug antibodies (ADAs). ADAs may be neutralizing antibodies (NA) that neutralize the activity of these therapeutic proteins, causing reduced efficacy [9].

In the case of vaccines, the ability to induce an immune response, immunogenicity, is the expected therapeutic effect.

Immunogenicity, being one of the significant concerns in relation to biologics, is assessed throughout their entire development and production process.

The ability of biologics to induce immune responses may depend on several factors: The particular properties of the biologic, the characteristics of the patient, the concomitant treatments, the routes and the features of administration, or, finally, any variations introduced in the manufacturing process [10].

It is known that in the 1990s, the replacement of serum albumin with stabilizing agents (polysorbate 80 and glycine) in epoetin alfa caused several cases of pure erythroid aplasia due to the development of antierythropoietin antibodies [11].

2.3 Biosimilarity

Biologics enjoy two protection mechanisms: Patent (usually lasting up to 20 years) and a period of data and market exclusivity (up to 11–12 years) [12].

Once this period of patent coverage and exclusivity is over, "biosimilars", non-identical but similar copies of originator biologics, determined to be of equal quality, safety, and efficacy to the originators, can be produced [13, 14].

"Biosimilarity" is the regulatory term first used by the European Union (EU) and the EMA to denote the comparability between a biosimilar and its originator reference medicine [13].

The first commercially available biosimilar appeared in the EU in 2006, while the first approval of a biosimilar in the United States (US) was in 2015 [15].

Medicinal products produced by biotechnology differ from traditional pharmaceutical chemistry methods in many aspects, including molecular size, structural complexity, stability of the final product, and the possibility of different relevant co- and post-translational modifications (e.g., of the glycosylation profile). Additionally, because of their production process, which involves the essential intervention of living systems (microorganisms or animal cells), biologics present numerous aspects of heterogeneity linked to the host cell used, the plasmids used to transfect the host cell, and, therefore, transfer the gene necessary to induce the expression of the desired protein, as well as the conditions of growth and fermentation and the different methods of purification. All these peculiarities are not immediately transferable from one laboratory to another and contribute to the uniqueness of the product [4]. In particular, changes in the glycosylation pattern, a process that naturally occurs during the formation of a protein, can affect the therapeutic effect of the drug as well as lead to pharmacokinetic and pharmacodynamic modifications, altering the final product [15].

Therefore, structural variability and nonexact identity are two problems already present in original biologics, between different batches of the same product or even between drugs of the same set, and not only linked to their copies, that is, the biosimilars. This is because the very concept of similarity and nonidentity, which underlies biologics and biosimilars, is due to the inherent inability to replicate biological molecules exactly [16].

However, the primary responsibility of regulatory authorities and manufacturers in this context is to avoid clinically significant structural differences, which could adversely affect the efficacy and safety of the proposed biosimilar. This is achieved by assessing and demonstrating a high degree of structural and functional similarity between the originator and the biosimilar through what is known as a "comparability exercise," via studies that are defined as "of comparability" or "comparative" [13].

Therefore, the registration process of a biosimilar is different from that of a nonbiological drug equivalent (for which only bioequivalence studies, showing pharmacokinetic parameters, are generally required) (**Table 1**).

The investigation of biosimilars starts with quality studies (biological and physicochemical) and then continues with comparison studies with the originator, initially nonclinical (comparative nonclinical studies), concerning toxicity, pharmacokinetics, and pharmacodynamics, and then clinical (comparative clinical studies), in which efficacy and safety are assessed. In addition, at least one clinical study of immunogenicity is required to compare this aspect between the biosimilar and the original biologic (**Figure 1**) [4, 17].

It is clear that since clinical efficacy studies have already been conducted for originators, the purpose of studies on biosimilars is not to establish clinical benefit, but to demonstrate clinical equivalence, that is, noninferiority, with the biologic originator, defined in terms of "similarity throughout."

2.4 Interchangeability and substitutability

"Interchangeability" is generally defined as the medical practice of substituting one drug for another equivalent drug with the same clinical effect and the risk–benefit ratio [18]. It thus describes the process, following a clinical decision by the prescribing physician, of transition from the originator to the biosimilar or from the biosimilar to the originator or between two biosimilars [13]. Interchangeability can only be assessed after the biosimilar has received regulatory approval.

"Substitutability," on the other hand, is defined as the practice, not necessarily of exclusive medical pertinence, of replacing medicine with another, often

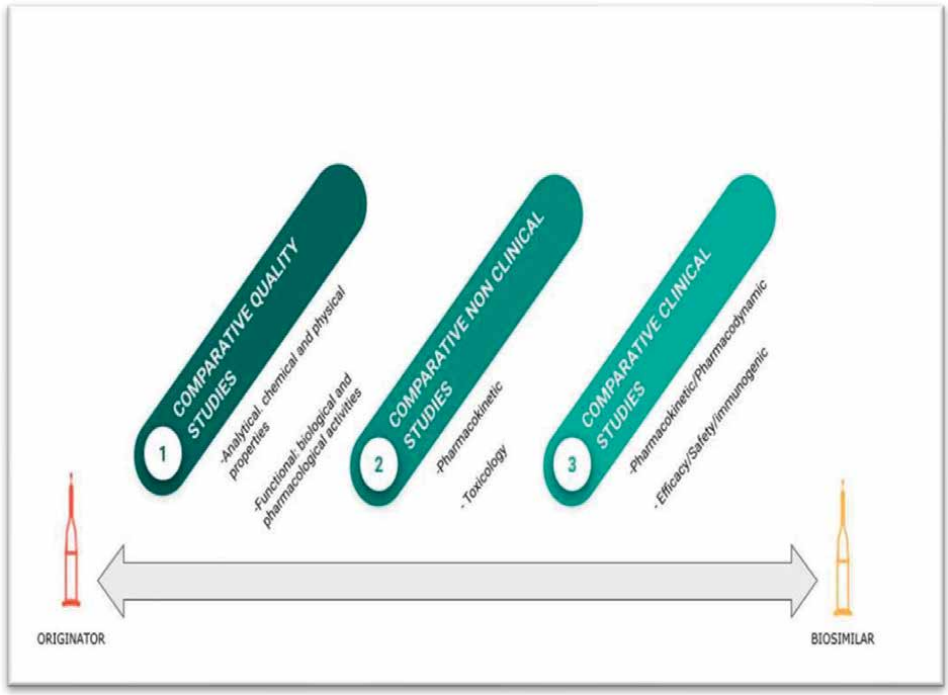

Figure 1.
Studies required for biosimilars.

cheaper, that has the same qualitative and quantitative composition of active substances, the same pharmaceutical form, and route of administration and which is bioequivalent with the reference medicine based on bioavailability studies [13]. "Automatic substitution" (for equivalents) by pharmacists refers to the practice whereby the pharmacist has the faculty or is obliged by national or local regulations, to dispense an equivalent and interchangeable medicine in place of the prescribed medication, without consulting the prescribing physician. "Primary substitution" occurs when a new treatment is started with a biosimilar (or equivalent) rather than the original reference product, and "secondary substitution" occurs when the treatment of a patient, already receiving a biologic, is substituted with a biosimilar [4].

However, it should be specified that in the US, the concept of interchangeability corresponds to the European concept of substitutability or "switching," since in the US, when the biosimilar is designated for use interchangeably with the original biologic, the pharmacist can dispense and authorize automatic substitution. Specifically, the Food and Drug Administration (FDA) requires that the definition of interchangeability of a biosimilar with the reference product must be established by an internal committee (the Biologics Price Competition and Innovation Act) based on specific documentation. To receive a designation of interchangeability in the US, the manufacturer must demonstrate through ad hoc studies that (1) the biosimilar will produce the same clinical outcome as the reference product in a given patient, and (2) the risk in terms of safety or reduced efficacy of alternating or switching between the use of the originator and the biosimilar is no greater than the risk of using the originator without such "switches" (**Figure 2**).

Thus, for the FDA, once a single biosimilar is defined as interchangeable, the clinician's decision on the individual case is not required for its substitution [18].

Regarding the automatic substitutability of biosimilars, the EMA does not assume responsibility for interchangeability and refers this decision to the EU Member States; in fact, European legislation has given the competent national authorities of the various Member States decision-making legislative autonomy in this matter (**Table 1**). However, the EMA has clarified that the recommendations issued on the marketing of medicinal products do not include whether or not a biosimilar should be used interchangeably and that the decision on the prescriptive choice of the specific medicinal product to be used, reference rather than biosimilar, should be entrusted to qualified healthcare professionals [19]. Moreover, the EMA generally recommends continuity of treatment for any patient already on therapy; but also emphasizes that there is no reason not to prescribe biosimilars directly to naive patients, that is patients who have not been treated previously, especially about the cost savings that this entails [4].

In European countries, several national regulatory authorities support substitutability during initial treatment or with the consent of the prescribing physician, but it is not endorsed unequivocally and uniformly [20]. In other countries, interchangeability is treated even differently than in the EU and US [1, 21]. Certifying that the drug is interchangeable is very complex for regulators without sufficient supporting data. The substitutability of generic drugs with reference drugs is used because the two drugs are considered identical if they have been demonstrated bioequivalence, but, as biosimilars are not exact copies, the generic approach cannot be applied in the case of biosimilars, and the question of their interchangeability remains unclear and is still an open debate that essentially involves all regulatory agencies.

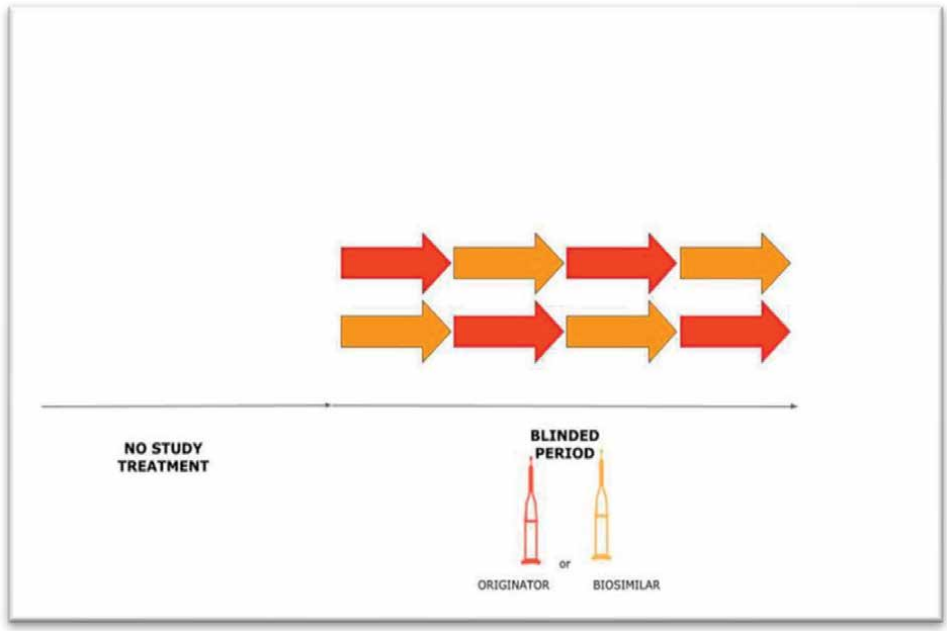

Figure 2.
Interchangeability studies. FDA requires evidence of a single "switch" for approval of a non-interchangeable biosimilar, but will generally require data on multiple "switches" for the definition of interchangeability.

Indeed, the main concern about interchangeability is that repeated switches between biosimilars and the reference biologic may increase immunogenicity, leading to adverse reactions, particularly therapeutic ineffectiveness.

2.5 Extrapolation

Extrapolation is a scientific rationale used to describe how the proposed biosimilar receives all of the approved indications from the originator while performing comparative clinical trials of only one or two signs [22]. This rationale is captured in confirmatory phase III clinical trials, although the results of each experimental phase affect the extrapolation of indications.

There are limitations if particular indications are still protected by patent.

This concept of transferability of safety and efficacy data from one indication to another is not always clear to prescribing clinicians. Still, the extrapolation of therapeutic indications is recognized by both the EMA and the FDA [23, 24], although there must be a valid scientific justification for it to be applicable.

It is up to the Committee for Medicinal Products for Human Use (CHMP) of the EMA in the EU and the FDA in the US to determine on a case-by-case basis whether multiple indications can be extrapolated based on sufficient scientific evidence [23, 24].

2.6 Pharmacovigilance of biologics: Specific aspects

For all drugs, and certainly also for biologics, which do not yet have an established history behind them, robust postmarketing surveillance is crucial for identifying and assessing adverse effects and any other issues under discussion, such as the rationalization of interchangeability itself. The current pharmacovigilance paradigm typical of the "small molecule drugs" is highly insufficient and unsuitable to monitor the safety of biologics and biosimilars due to the different manufacturing techniques and the typical complexity of biologics, the possible structural differences existing between biosimilars and their originators, the possibility of biologics to cause long-term or short-term immunological reactions. Biologics are considered a priority for pharmacovigilance activities and, for this reason, the Directive 2010/84/EU included them in the "List of medicines subject to additional monitoring," characterized by an inverted black triangle in the "summary of product characteristics" (SmPC) and package leaflet accompanied by a sentence encouraging healthcare professionals and patients to report any suspected adverse reaction (**Table 1**) [25]. The EMA adopted new recommendations for the pharmacovigilance of biosimilars in 2016, and it has a separate section for "biological medicinal products" [26]. On the other hand, the FDA includes the Center for Drug Evaluation and Research (CDER), which is responsible for the pharmacovigilance of biosimilars and has its own guidelines [27, 28]. In the EU, all marketing authorization applications for biologics, including biosimilars, are reviewed by the EMA through a centralized procedure; consequently, the resulting marketing authorization is valid in all EU Member States. For this procedure to be undertaken, it is first necessary that the reference product, to which the application for marketing authorization of a biosimilar product relates, is a medicinal product that has obtained a marketing authorization in the EU based on a complete registration dossier, by Article 8 of Directive 2001/83/EC (**Table 1**) [13]. Each company must submit a risk management plan (RMP) with the marketing authorization application. The EU-RMP must detail the risk management system, describing the safety profile of the medicine, also taking into account the known safety profile of the corresponding originator, and

outline how the manufacturer will continue to monitor the efficacy and safety of its product and the measures that the marketing authorization holders (MAHs) intend to introduce to prevent or minimize any risk during the use of the medicine. Every biosimilar on the market has an ongoing EU-RMP, with a summary published in the European public assessment report (EPAR) (**Table 1**). Finally, Directive 2010/84/EU stipulates that marketing authorization may be conditional on post-authorization safety (PASS) and efficacy (PAES) studies. PASS studies aim to identify, characterize, and quantify a safety risk, confirm the safety profile of the drug, or even measure the effectiveness of risk management measures taken during the marketing of the drug (this includes, specifically, immunogenicity phenomena that represent a crucial safety issue for any biologics and are mandatorily managed in the EU-RMP). In contrast, PAES studies aim to assess and confirm efficacy in cases where there are uncertainties regarding some aspects of the effectiveness of medicine [4].

The nomenclature is also a particular aspect of pharmacovigilance of biologics. When only the international nonproprietary names (INN) are used to report biologics or biosimilars without a distinguishable identifier, it may be complex to attribute an adverse event to a specific product. Instead, each biosimilar should be easily differentiated from the reference product and other biosimilars to ensure the appropriate use, traceability, and accurate reporting of adverse drug reactions (ADR). Since 2006, the World Health Organization (WHO) has been looking for a name for biosimilars that is universal and more suitable than INN names. In the EU, using an INN is up to the manufacturer, and there is no specific legislation outlining how to name a biologic/biosimilar. As required by European legislation, all authorized medicines must have a trading name, either a brand name or the name of the active substance, followed by a trademark or the company's name that holds the marketing authorization. Therefore, each biologic, including biosimilars, is identifiable by a unique name formally approved by the EMA as part of the authorization process. In the EU, the reporting of suspected ADRs requires the inclusion of the brand name of the biologic and its batch number, but it has been shown that only 5% of ADRs include both the brand name and the batch number [29]. The lack and omission of traceable information can delay identifying safety problems with a specific product [30, 31]. The FDA, in 2019, has recently adopted a new guideline for the nomenclature of biosimilars, whereby four lowercase letters must be added as a biologic qualifier to the INN in the case of biosimilars [32], for example, Filgrastim-sndz. This action could promote an accurate identification of biologics and facilitate pharmacovigilance, increasing patient and physician confidence in biologics and biosimilars by ensuring proper traceability [31].

Another pharmacovigilance issue specific to biologics is, as already mentioned, immunogenicity (see Paragraph 2.2). Intrinsic differences may cause different immunogenicity even within the same batch. The immune response can be humoral (producing ADA is neutralizing or non-neutralizing) or cellular. Anaphylaxis and hypersensitivity reactions are the two main safety issues due to immunological reactions to these drugs. Still, even cross-reactivity to endogenous proteins or lack of efficacy or alternated drug pharmacokinetics may occur [33].

Such immunogenic ADRs, and even more so those due to immunogenicity linked to the "switch" (between an originator and a biosimilar or vice versa or between a biosimilar and another biosimilar), are difficult to identify they may occur in a minimal number of patients. It is also essential to understand the time interval between the administration of biologics and the occurrence of adverse events because of the possibility of delayed immunogenic reactions, which create further serious difficulties in defining the causal relationship with the specific product. Full characterization of

immunogenicity cannot be established during approval studies but requires long-term studies and rigorous postmarketing surveillance.

3. Conclusions

The pharmacovigilance of biologics undoubtedly presents complexities that are not unique to "conventional drugs." It is an evolving science that will undoubtedly need to be implemented since knowledge about these drugs continues to expand. The peculiarities of these drugs make the monitoring of biologics and biosimilars a real challenge for regulatory agencies, manufacturers, and patients. Specific aspects of these drugs are immunogenicity, differences between batches from different manufacturers, and the definition of similarity and interchangeability or substitutability, all of which are undoubtedly important for the safety and the pharmacovigilance of these drugs [34]. An emblematic example is the number of cases between 1998 and 2004 of pure erythroid aplasia caused by autoantibodies due to a manufacturing modification that increased the immunogenicity of an erythropoiesis-stimulating agent [11, 35]; however, with three similar products on the market, the real challenge was to identify which specific agent was causing the problem [36]. As is well known, the development of biosimilars not only reduces the cost of healthcare by reducing drug costs by 20–30% [37] but also increases the number of marketing authorizations and consequently the access to such therapies, as demonstrated by a study on 21 European countries that showed that the average cost of erythropoietin fell by 35% from 2006 to 2013 [3]. Yet, as highlighted by a recent review [6], healthcare professionals still approach biosimilars with great caution and sometimes stigmatization, and, in particular, are generally opposed to multiple "switches" and interchangeability. Moreover, many treatment discontinuations with biosimilars seem to be linked to the nocebo effect [38]. Clinicians should, however, take into account the principle that no two biologics are identical, even if they are produced by the same manufacturer, as each biologic is different from another in itself [39]; they should also consider that regulations on biosimilars (unlike those on generics) are stringent and rigorous and this in itself is a guarantee (although not a certainty) of high-quality standards. Healthcare professionals and patients should, therefore, have a coherent, comprehensive, and unbiased view of the biosimilar. Still, to do so, their knowledge needs to be updated appropriately through effective and continuous training programs promoted by the various national regulatory agencies. Nevertheless, it is also necessary to collect more and more reassuring data on biologics in general and on interchangeability (and the possible induction of immunogenicity related to it), which is still the central dilemma among clinicians and stakeholders. It is also essential to consider that immunogenicity could be a consequence of several factors, such as the underlying disease, genetic background, age, and immune status, including immunomodulatory therapy, route of administration, dosing schedule, frequency, and duration of treatment, post-translational modifications, formulation, and impurities. Finally, it is essential to develop educational tools regarding the ADR reporting process for biological products, including the appropriate use of the specific product name and batch number, and reflect on the possibility of making such data more easily accessible to the clinician/or pharmacist.

Conflict of interest

The authors declare no conflict of interest.

Acronyms and abbreviations

EMA	European Medicines Agency
ADA	antidrugs antibodies
NA	neutralizing antibodies
EU	European Union
US	United States
FDA	Food and Drug Administration
CHMP	Committee for Medicinal Products for Human Use
SmPC	summary of product characteristics
CDER	Center for Drug Evaluation and Research
RMP	risk management plan
MAHs	marketing authorization holders
EPAR	European public assessment report
PASS	post-authorization safety studies
PAES	post-authorization efficacy studies
INN	international nonproprietary names
ADR	adverse drug reaction
WHO	World Health Organization

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Chapter 6

Machine Learning Applications in Pharmacovigilance: Scoping Review

Hager Ali Saleh

Abstract

Background: Pharmacovigilance (PV) is the activity to identify comprehensive information on the safety characteristics of the drug after its marketing. The PV data sources are dynamic, large, structured, and unstructured; therefore, the automation of data processing is essential. Purpose: This review aims to identify the machine learning applications in PV activities. Methods: Nine (9) studies that were published within the period from 2016 to 2020 were reviewed. The studies were extracted from two databases; PubMed and web of science. The review and analysis were done in December 2020. Results: The supervised and semi-supervised learning techniques are applied in the main three PV group activities; adverse drug reactions (ADRs) and signal detection, individual case safety reports (ICSRs) identification, and ADRs prediction. Future research is needed to identify the applicability of unsupervised learning in PV and to formulate the legal framework of the false positive predicted data.

Keywords: machine learning, pharmacovigilance, supervised learning, semi-supervised learning, unsupervised learning

1. Introduction

The World Health Organization's (WHO) definition of pharmacovigilance (PV) is "the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problem" [1]. It is difficult to get comprehensive safety characteristics of the drug during the drug development phase because the clinical trials are conducted in a controlled environment in a limited patients number and for a specific duration, however, after the drug marketing, it will be prescribed to thousands of patients in different age groups, therefore, it is obligatory that "safety of all medicines to be monitored throughout their use" [2].

In 2018, the WHO global database of individual case safety reports (VigiBase) has 17 million ADRs reports [3] and the Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) has more than 10 million of which 5 million are serious ADRs and one million caused the death [4]. These databases use spontaneous reporting to collect ADRs, nevertheless, the known criticisms of spontaneous

reporting are under-reporting and uncertainty of the causality assessment[1] [5], therefore, there is a need to find other methods to predict ADRs and to efficiently analyze the available data not only from the structured data from spontaneous reporting databases (SRS) but also from other data sources, such as electronic health records (EHR), clinical narratives, medical literature, social media, and health forums [6].

The PV data sources are dynamic, diverse, structured, and unstructured, accordingly, the manual detection of ADRs and processing of PV data are time-consuming, therefore, the automation of ADRs/signal detection and reports processing will be efficient [7].

Machine learning (ML) is a robust data analysis technique that has statistical and probabilistic techniques to develop models that automatically learn from data and consequently help to accurately identify and predict the source data [8]. ML algorithms are supervised, unsupervised, and semi-supervised learning. In supervised learning, a known label is used to train a model to predict labels from new data, while the unsupervised mathematical methods are used to cluster data, and semi-supervised uses models based on both [8].

This scoping review aims to explore the current applications of machine learning techniques on pharmacovigilance (PV) activities; therefore, the research questions are:

- What are the PV activities and data sources for which the machine learning techniques are currently applied?
- What are the machine learning methods used?

2. Methods

The scoping review was considered to explore the available publications regarding the current applications of machine learning techniques in pharmacovigilance activities. The literature search was performed in December 2020.

2.1 Sources

PubMed and web of science were considered to identify relevant publications related to machine learning and pharmacovigilance. PubMed focuses on the life and the biomedical sciences, while the web of science covers medical and computing and information technology. Boolean operators were used to define the relationship between keyword and Wildcard symbols that were used to expand the scope of the search [9, 10].

2.2 Search criteria

- *Inclusion criteria*: Journal articles in the English language and articles published between 2016 and 2020.
- *Keywords*: The keywords for PubMed are ("machine learning"[MeSH Terms] OR ("machine"[All Fields] AND "learning"[All Fields]) OR "machine learning"[All

[1] Causality assessment of the ADRs is "method used for estimating the strength of relationship between drug exposure and occurrence of adverse reaction(s)" [5].

Fields]) AND ("pharmacovigilance"[MeSH Terms] OR "pharmacovigilance"[All Fields]). While The keywords for the web of science are TOPIC: (machine learning) AND TOPIC: (pharmacovigilance). The number of hits in each database and the total number of hits obtained after applying the filters are shown in **Table 1**.

2.3 The articles selection

All the articles found in the two bibliography databases were reviewed, the duplicate check was done, and 21 duplicates were detected and removed. After that, the remaining

Keywords	PubMed	Web of Science
machine learning AND pharmacovigilance	93	84
After Applied Filters		
Filters: in the last 5 years, Humans, English	50	—
Languages: (English) And Document Types: (Article) Timespan: Last 5 years. Indexes: SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI.	—	46
Total	96	

Table 1.
Shows the number of hits per database.

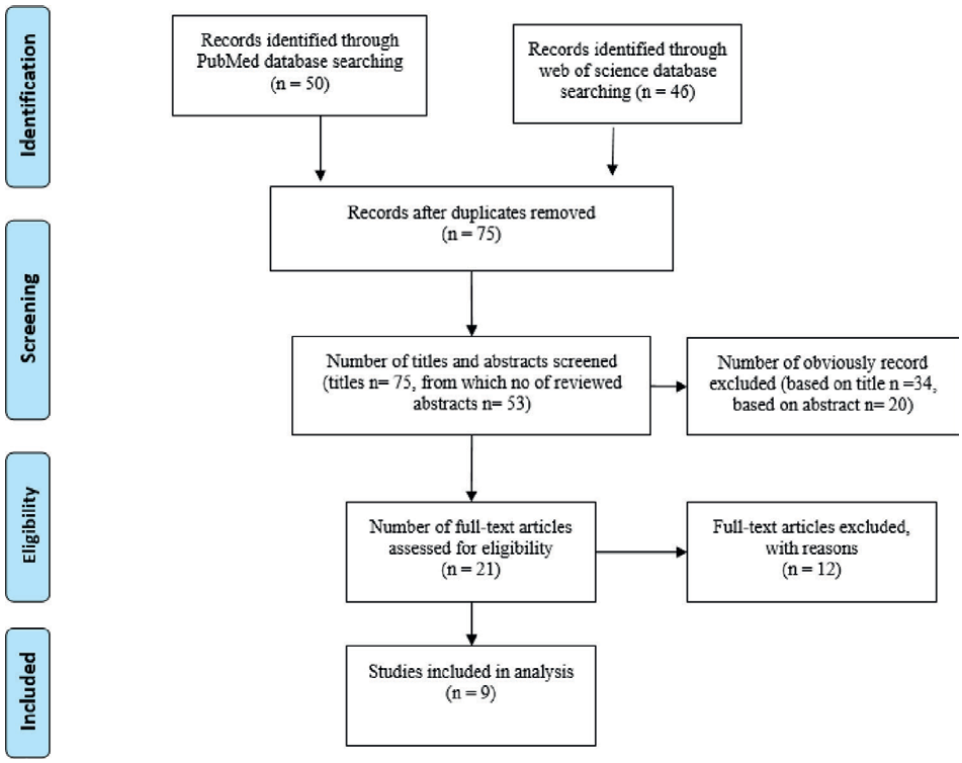

Figure 1.
PRISMA diagram for the articles' selection process.

hits were assessed. The inclusion criteria were peer-reviewed and relevant articles, the relevance means articles that clearly addressed the ML application in PV activities, while the exclusion criteria were articles that addressed PV alone, articles addressed the use of ML in drug-drug interaction (DDI) detection because DDI is not the focus of PV activities, and articles focused on considering more data sources rather than ML Applications.

The hits assessment process was done in three phases firstly assessment of the title, then an assessment of the information provided by the abstracts, eventually assessment of the full text. At each phase, articles were retained or excluded for analysis, based on the inclusion and exclusion criteria. PRISMA flow diagram was used to illustrate the selection process (**Figure 1**) [11].

3. Results

3.1 Overview of articles characteristics

A total of 96 articles were identified of which nine articles met the inclusion criteria, seven were research articles and two reviews. **Table 2** summarizes the retrieved articles according to the year of publication, the first author, the country where the author affiliation is located, the PV activities and data sources, ML technique, and the main findings.

3.2 The PV activities and ML

Based on analyzed articles ML techniques are used in their PV activities groups. Early detection of ADRs and signal detection, individual case safety reports (ICSRs) identification, and ADRs prediction.

3.3 Early detection of ADRs and signal detection[2]

3.3.1 Spontaneous reporting systems mining

From the last quarter of 2012 to the second quarter of 2013, 632 722 data were extracted from FAERS reports by using the Apriori algorithm 2933 interacting f drug interaction-adverse event was extracted. The algorithm was effective to detect severe life-threatening and rare ADRs [6].

3.3.2 Electronic health record mining

Discharge summaries mining: The supervised machine learning technique was used to detect the ADRs from discharge notes in a tertiary hospital in Switzerland by using a hybrid method, ML, and rule-based. The manual annotation was used to create the training and testing datasets, while the supervised learning technique is used to classify the discharge notes as positive (had ADRs) or negative (had no ADRs), the automatic detection was efficient compared to the manual one and the accuracy was 0.90 [12]. Furthermore, ML algorithms were used to automate the detection of the relationship between the drug and the ADR from the discharge summaries [14].

[2] "A signal is defined by WHO as reported information on a possible causal relationship between an adverse event and a drug" [19].

RN	Year	Author	Country	PV activity/ Data source	ML method/ Concept	Main findings
[12]	2020	Vasiliki Foufi	Switzerland	Early detection of ADRs (from Discharge Letters mining)	Supervised learning for the text classification. The following ML algorithm is used: Support Vector Machine (SVM), Naive Bayes Classifier, and Linear Classifier. Where 20% of the dataset is used for testing, while 80% is used for training.	ML algorithms are efficient to detect automatically the ADRs. Naive Bayes Classifier and Linear Classifier have more accuracy than the SVM the accuracy was (0.94, 0.94, and 0.83, respectively)
[13]	2019	Azadeh Nikfarjam	USA	Signal detection (from health forums)	"DeepHealthMiner (DHM), a neural network-based named entity recognition (NER) system" where the supervised learning was used to train the DHM to identify the ADRs	13600 ADRs were detected where the F-measure was 0.738 (0.731 precision and 0.745 recall).
[4]*	2019	Anna O. Basile	USA	Early detection of ADRs (from literature)	the ML models were used to predict ADRs from literature and to detect ADRs from EHRs. Natural Language Processing (NLP) is used to detect ADRs from clinical notes and social media.	The limitation of the SVM is the prediction of unknown ADRs cannot depend on the labeled data.
[14]	2019	Yixuan Tang	Singapore	Early detection of ADRs (From EHR)	A rule-based approach called Readpeer for Active PV (REAP) this structure divided into two steps "named entity recognition (NER) and drug-AE relation extraction" where the ADRs and drug names were recognized then the pairing of ADR-Drug would occur.	The precision and recall of ADRs and drug name detection were 90%. While for detection the relationship between the drug and the ADR the precision was 75% and the recall was 60%.
[6]*	2019	Chun Ye n Lee	Australia	Signal detection (SRS and social media)	using the Apriori algorithm to detect life-threatening ADRs from FAERS reports. SVM classifier to detect from Twitter posts if the users used the drug and to detect the ADRs mentioned in the posts.	The precision of the Apriori algorithm was 85% and sensitivity was 81%. The precision of the SVM classifier was 70%, while the recall was 69%
[15]	2018	Shaun Comfort	USA	ICSR identification (from social media)	Support vector machine (SVM) algorithm used to detect ICSRs from 311,189 social media posts	The ML model spent 48 hr. to finish the task compared to an estimated 44,000 hr. spent by human experts and the accuracy was 74%.

RN	Year	Author	Country	PV activity/ Data source	ML method/ Concept	Main findings
[16]	2018	Shashank Gupta	India	Early detection of ADRs (from social media)	Semi-supervised bidirectional long-short-term-memory (LSTM) where the unsupervised technique is used to train the bidirectional-LSTM model to predict the drug name, and the supervised model to retrain it to predict the label sequence.	The semi-supervised was effective, where the F-score was 0.751.
[17]	2017	Kalpana Raja	USA	Adverse drug reactions prediction (Literature mining)	The researchers used the DDI corpus training data, the following classifier Bayesian network, decision tree, random tree, random forest, and k-nearest neighbors are used to predict ADRs types from the DDI corpus then the performance of each classifier was evaluated using 10- fold cross-validation technique. The random forest showed the best performance (F score = 0.9) After that, the researcher used this ML framework to predict from the literature the ADR types related to psoriasis.	The researchers identified the previously known ADRs (F score =0.9) and predicted the ADRs of psoriasis drugs.
[18]	2016	Vassilis Plachouras	UK	Detection of ADRs (From social media)	SVM classifier identified ADRs based on the surface-textual properties and the known information about drugs' adverse effects.	Accuracy = 74%

*RN= reference number, Year = Publication year, Author= First Author, and *= review articles*

Table 2.
Shows an overview of the eligible articles listed chronologically.

3.3.3 Social Media and Health forums mining

A combination of supervised and unsupervised ML models (semi-supervised) was used to detect the ADRs mentioned in Twitter posts, where the unsupervised trained model to detect the drug name, while the supervised technique was to retrain the model to detect the ADRs labels [16]. Furthermore, 67172 posts are identified in the health forums, where 13600 ADRs were identified by using the supervised machine learning technique [13].

3.4 ICSR identification

3.4.1 Social media mining

The ICSR to be valid it should have identified the patient, identified the suspect drug, identified ADR, and identified the reporter, so to identify the valid or invalid ICSR from social media posts "ICSR classification framework" was developed by using a support vector machine (SVM) to detect the patient, drug, and ADR, while the reporter was assumed to be the author of the post [15].

3.5 ADRs prediction

3.5.1 System pharmacology

System pharmacology is "the study of drug action using principles from systems biology, considering the effect of the drug on the entire system rather than a single target or metabolizing enzyme." Its application to PV activities is to focus on "off-target effects and clinical observations of adverse reactions." [4] An application of this approach was addressed in a published study in 2017, where the researchers evaluated the feasibility of using the "ML models to learn syntactic and semantic information from literature," to enhance the model prediction the researchers used drug-drug interaction (DDI) information to predict ADRs caused by DDI, and drug-gene interaction (DGI) to predict the ADRs caused by two drugs interaction by the same gene [17].

3.5.2 Event reporting system database mining

The Bayes classifier algorithm was used to predict ADRs from experts' opinions texts in the ADR case [4].

4. Discussion

Based on the reviewed literature, the benefits of integrating ML with PV activities are the following:

4.1 The data source for post-marketing surveillance

There are two data sources[3] structured for example spontaneous reporting systems (SRSs) and unstructured like medical literature, clinical notes, and social media

[3] Post marketing surveillance "refers to the process of monitoring the safety of drugs once they reach the market" [20].

posts [6]. The ADRs are collected by regulatory authorities through voluntary reporting to SRSs, therefore, under-reporting is the main drawback of these sources, therefore, it is important to use more data sources to comprehensively collect the safety information [6]. The supervised and semi-supervised machine learning techniques helped in mining other data sources, such as clinical notes, medical literature, and social media [4, 6, 9, 10, 12–14].

4.2 Improve the accuracy and time efficiency

The PV sources are dynamic, which means it is periodically updated over time, these sources become large beside their unstructured characteristics [6], and the accuracy of using ML techniques in the detection or prediction of ADRs was between 74% to 90% [6, 9, 12], the precision was between 0.7 and 0.9 [10, 11], furthermore, the ML model spent 48 hr. to finish the ICSR identification task from social media compared to an estimated 44,000 hr. spent by human experts with accuracy 74% [12].

4.3 ADRs prediction

Predicting ADRs in the early stages will enhance drug safety activities and reduce the financial cost, for example, saving the cost of hospitalization due to the ADRs [21], the ML techniques were used to predict the ADRs from the social media posts, F score=0.9 [14].

4.4 Limitation of the review

Only two databases are considered, the scoping review is not like the systematic review, therefore, it is expected to miss some relevant articles.

5. Conclusion

The supervised and semi-supervised machine learning techniques are applied in the main three PV group activities; detection of adverse drug reactions (ADRs) and signal detection, individual case safety reports (ICSRs) identification, and ADRs prediction. Furthermore, it helps in analyzing large data sources, such as social media and literature, to predict and detect ADRs, accordingly, it complements the drawbacks of spontaneous reporting. Moreover, ML techniques are efficient in terms of accuracy and saving time when compared to human experts.

Knowledge gaps

The supervised learning technique is currently used in PV activities, which has a problem with the scarcity of labeled data [16], so the first knowledge gap is how to apply the unsupervised technique in PV activities.

The second knowledge gap is that PV activities are legally regulated [22], therefore, a regulation should be developed to manage the risk of false-negative detected results.

The third knowledge gap: further research is needed to assess the attitude, knowledge, and practice of PV personnel regarding the applicability of the ML techniques in PV daily practice.

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Conflict of interest

The author declares no conflict of interest.

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Section 2

Signal Detection

Chapter 7

Early Signal Detection: Data Mining of Mental Disorders with Statins

Maria-Isabel Jimenez-Serrania

Abstract

Statins are widely prescribed to treat dyslipidemias. It is well-known adverse reaction of these active ingredients related to rhabdomyolysis and myalgia, but there are other signals to be aware of, such as mental disorders. Pharmacovigilance tools help to trace known risks and detect early other unknown effects that appear over time. Data of all the reported suspected adverse drug reactions for statins from the international World Health Organization (WHO) repository Vigibase were analyzed with an adaptation of data mining Bayesian methodology to search for positive signals, threshold of false discovery rate (FDR) < 0.05, and listed candidates for priority clinical investigation. Among positive mental signals observed, some were currently stated as adverse reactions in technical factsheets as insomnia, depression, dementia, and nightmares, but others have not reached this condition as bipolar, psychotic, and emotional disorders or symptoms and suicide. Other diverse central positive signals that can be confounded with mental conditions obtained and not stated were senses impairment, such as blindness, deafness, balance disorder, and events related to suicide. Worrying positive signals proposed as candidates to further investigation are insomnia for pitavastatin, pravastatin, and simvastatin; dementia for atorvastatin and rosuvastatin; and suicide and psychotic disorders for atorvastatin, lovastatin, pravastatin, rosuvastatin, and simvastatin.

Keywords: statin, adverse reaction, mental disorders, data mining, positive signals

1. Introduction

Statins or 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitors are a worldwide used medication for dyslipidemias, both hypercholesterolemia, and hypertriglyceridemia [1].

These drugs are considered safe and cost-effective, but it is necessary to review the use and possible risk of adverse events. Some frequent adverse drug reactions (ADRs) related to statins affect muscle (myalgia, arthralgia, limb pain, and spasms), liver (elevation of transaminases or creatine kinase), and gastrointestinal system (constipation, flatulence, dyspepsia, nausea, and diarrhea) and are related to infections (nasopharyngitis) [2, 3].

ADRs related to musculoskeletal and connective tissue, such as myopathy, rhabdomyolysis, or myositis, are classified as rare [3]. The withdrawal of cerivastatin in

2001 was due to deaths attributed to drug-related rhabdomyolysis that led to kidney failure [4].

However, besides, there is a group of ADR related to mental status, cataloged as rare or very rare or frequency not known such as insomnia, sleep disorders, depression, cognitive impairment, memory impairment, and nightmares [3, 5]. Some of these events can be confusing and wrongly identified in older patients with mental deterioration [6].

This study aims to make available an early knowledge of signals of statins' adverse reactions related to mental disorders to analyze in future clinical trials and provide a list of candidates for clinical trials.

2. Materials and methods

Nowadays, free access to national and international reporting ADR databases allows investigating new signals to be aware of possible risks. One of them is VigiBase®, the unique World Health Organization (WHO) global database for suspected ADRs maintained by the Uppsala Monitoring Centre (UMC) since 1968. This database disposes of a free-user interface VigiAccess™ that allows us to search for all data coming from over 110 countries, undersigning a statement of the responsibility for the appropriate use and interpretation of data [7].

For the present study, reported data of all the ADRs related to the chemical subgroup of the Anatomical Therapeutic Chemical (ATC) Classification System C10AA "HMG CoA reductase inhibitors" known as statins were searched in VigiAccess™ [8]. Data below the first heading adverse drug reactions (ADRs) for each active ingredient of interest—atorvastatin, cerivastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin, and pitavastatin—were extracted on October 2, 2019. Signals for cerivastatin—withdrawn in 2001—are included and analyzed as of contrast.

In this database, it is not possible to calculate the frequency of any ADR, but the data mining methodology, Bayesian confidence propagation neural network (BCPNN), can be used in these situations [9]. Nevertheless, this methodology is developed and used by the UMC as the WHO Collaborating Centre for International Drug Monitoring [10–12].

To detect signals of ADR, this method BCPNN was improved, by the UMC of the WHO with an extension to the multiple comparison settings. The calculated Bayesian estimator of false discovery rate (FDR) works like a p-value, offering a positive signal if FDR < 0.05 [13, 14].

An adaptation of this methodology can be plausible as same as other diverse methods can be trustworthy in global adverse drug reaction surveillance with a correct interpretation of the signals [15]. This one consists of contrasting all the ADRs of the ATC subgroups instead of all the pairs of ADR-drugs of the database. In this case, only the chemical subgroup C10AA "HMG CoA reductase inhibitors" [16] was considered in the analysis. This methodology approach has previously demonstrated robustness and consistency when all the ADR databases were applied to a specific group of drugs [17–19]. Details of the algorithm performed are reported (see Appendix 1).

All the positive signals among statins were obtained. Those related to mental disorders were extracted and grouped depending on the presence of the ADR in the summary of product characteristics (SPC) of each active ingredient implied and categorized according to high-level terms (HLTs) including preferred terms (PTs) of

the Medical Dictionary for Regulatory Activities (MedDRA) [20], the standard terminology used in VigiAccess™.

The first aggrupation for statin positive signals obtained (FDR < 0.05 and Sp ≥ 0.99) was related to similar pathology following MedDRA, e.g., insomnia (that include general, middle, terminal, sleep disorder, and poor quality of sleep) and depression (that include general, major, depressed mood, and depressive symptoms) (see Appendices 2 and 3).

Finally, a ranking of positive signals for each statin is proposed as a list of priority ADR to further study.

The R® free software v3.4.1. R [21] and PhViD® Package v1.0.8 [22] were used to implement the methodology and to obtain positive signals. All the searches of evidence were made in the Medline database via Pubmed® [23].

3. Results

The total of positive signals with FDR < 0.05 and Sp ≥ 0.99 were 493, being 47 out of them related to a mental disorder (or confounding central symptoms): seven for atorvastatin (14.9%), three for fluvastatin (6.4%), three for lovastatin (6.4%), three for pitavastatin (6.4%), five for pravastatin (10.6%), eight for rosuvastatin (17.0%), and 29 for simvastatin (29.8%). All the results of algorithms related to a mental disorder and other confounding central disorders observed are available (see Appendices 2 and 3).

Subgroups of positive signals were second stratified and summarized considering the presence/absence of ADR in the summary of product characteristics. Mental disorders detected and reported in technical factsheets were insomnia, depression, dementia, and nightmares (**Table 1**), and not reported disorders were anxiety, bipolar disorder, and psychotic or emotional disorders/symptoms (**Table 2**). Finally, other diverse symptoms were identified to a greater or lesser extent with mental affectation

Statin	Insomnia and related	Depression and related	Dementia and related	Dreams disorders and related
Cerivastatin		6		
Atorvastatin	2*		10*, 11, 12, 13	
Fluvastatin	1*, 4*			14*
Lovastatin		7*		
Pitavastatin	1*, 2, 3			
Pravastatin	1*, 4*, 5			14*, 15
Rosuvastatin	4*	8*	11, 12, 13*	16
Simvastatin	1*, 4*, 5	7*, 8*, 9*		14*, 15

1, insomnia and related (general); 2, middle insomnia; 3, terminal insomnia; 4, sleep disorder; 5, poor quality sleep; 6, depression (general); 7, major depression, 8, depressed mood; 9, depressive symptoms; 10, amnesia; 11, dementia (general); 12, dementia Alzheimer's type; 13, memory impairment; 14, nightmares; 15, abnormal dreams; 16, daydreaming.
Sensitivity ≥0.20.
**Stated in the summaries of product characteristics (SPCs).*

Table 1.
Positive signals (FDR < 0.05; specificity ≥0.99) for statins related to mental disorders reported as ADR in Vigiaccess™.

Statin	Loss of special senses	Disturbance of special senses	Other mental health problems	Suicide
Cerivastatin			15, 20, 21	
Atorvastatin	1, 2, 3*, 4*, 7	11*, 13*	21	22
Fluvastatin				
Lovastatin	1, 3, 6	8, 9, 14 *	19	22
Pitavastatin		12		
Pravastatin	5, 6	8*, 9, 11*, 12, 13, 14		
Rosuvastatin	2, 4	10	16, 17	24
Simvastatin	6,7		18, 19	22, 23, 24, 25

1, bilateral blindness; 2, unilateral blindness; 3, bilateral deafness; 4, unilateral deafness; 5, anosmia; 6, ageusia; 7, balance disorder; 8, diplopia; 9, visual impairment; 10, visual acuity reduced; 11, vision blurred; 12, sudden hearing loss; 13, tinnitus; 14, dysgeusia; 15: anxiety; 16, bipolar disorder; 17, bipolar I disorder; 18, psychiatric symptom; 19, psychotic disorder; 20, emotional disorder; 21, emotional distress; 22, complete; 23, attempt; 24, ideation; 25, behavior. Sensitivity ≥0.20.
**Stated in the summaries of product characteristics (SPCs).*

Table 2.
Other positive signals (FDR < 0.05; specificity ≥0.99) for statins related to central or other mental disorders reported as ADR in Vigiaccess™.

such as impairment of senses (blindness, deafness, and vision blurred), and compromised life (suicide) (**Table 2**).

If we perform a list of positive signals (FDR < 0.05; specificity ≥0.99; and sensitivity ≥0.20 and < 0.20) not stated in the factsheets of each active ingredient, differences among drugs are detected (**Table 3**). These all are candidates to be deeply studied in clinical trials. In addition, in terms of the number of reports, the most relevant signals with the highest number of pair [active ingredient-ADR] reports were simvastatin-ageusia (85 reports) and rosuvastatin-unilateral deafness (21 reports). Less sensitive signals, but alarming, were the pairs simvastatin-ADR related to suicide (477 reports), pravastatin-affectation of senses (375 reports), atorvastatin-affectation of senses (693 reports), and lovastatin-complete suicide (50 reports).

There are three signals reported in SPCs with an elevated number of pairs of ADR-drug counted: atorvastatin-amnesia with 1360 reports and simvastatin-insomnia with 1210 (see Appendix 2) and for the withdrawn cerivastatin-anxiety 2767 (despite being withdrawn since 2001) (see Appendix 3).

The fact to include all the statins (also the withdrawn cerivastatin) and all the ADRs reported for statins acts as a contrast to the method used. Positive signals of ADR that lead to the withdrawal of cerivastatin (i.e., rhabdomyolysis and transaminases increased) and typical ADR related to statins (i.e., myalgia and myopathy) are also detected (see Appendix 4).

4. Discussion

This is the first study of mental adverse drug reactions (ADRs) related to statins using neural networks based on the principles of Bayes law. Owing to there being no evidence of similar studies, not even with the classical Bayesian methodology BCPNN, it is necessary to review the background to establish a starting point to further investigation.

Statin	ADR
Atorvastatin	Dementia (amnesia/dementia/Alzheimer/memory impairment)
	Loss of special senses (bilateral blindness/ unilateral blindness, balance disorder)
	Other mental health problems (emotional distress)
	Suicide (complete)
Lovastatin	Loss of special senses (bilateral blindness/ bilateral deafness/ageusia)
	Disturbance of special senses (diplopia/visual impairment)
	Other mental health problems (psychotic disorder)
	Suicide (complete)
Pitavastatin	Insomnia (middle insomnia)*
	Insomnia (terminal insomnia)
	Disturbance of special senses (sudden hearing loss)*
Pravastatin	Insomnia (poor quality sleep)
	Dreams disorders (abnormal dreams)
	Loss of special senses (anosmia/ageusia)
	Disturbance of special senses (visual impairment/sudden hearing loss/tinnitus/dysgeusia)
Rosuvastatin	Dementia (general/Alzheimer)
	Dreams disorders (daydreaming)*
	Loss of special senses (unilateral blindness)
	Loss of special senses (unilateral deafness)*
	Disturbance of special senses (visual acuity reduced)
	Other mental health problems (bipolar disorder/bipolar I disorder)
	Suicide (ideation)
Simvastatin	Insomnia (poor quality sleep)
	Dreams disorders (abnormal dreams)
	Loss of special senses (ageusia)*
	Loss of special senses (balance disorder)
	Other mental health problems (psychiatric symptom/psychotic disorder)
	Suicide (complete/attempt/ideation/behavior)

**FDR < 0.05; Specificity ≥0.99; Sensitivity ≥0.20/FDR < 0.05; Specificity ≥0.99; Sensitivity <0.20.*

Table 3.
List of early positive signals of mental (or central related) disorders detected for each statin agent and proposed to priority clinical investigation.

4.1 Positive mental disorders mainly presented as ADRs in SPCs

4.1.1 Insomnia

Some studies reported insomnia with a higher frequency for statins compared with all other drugs [24], but this risk of insomnia with statins seems to be not significant

for other studies of neuropsychiatric adverse effects of statins [25]. At the same time, multimethodological approaches using different algorithms and databases strongly suggest that statin use is associated with an increased risk for sleep disturbances including insomnia [26].

The situation of insomnia can lead to a loss of adherence to the treatment, more worrying in the elderly because they are less capable of sleeping correctly and can lead to polymedicate with sleep medicines [27].

In the present study, the positive signal of middle insomnia obtained with atorvastatin appears as the most relevant and already stated in SPCs, followed by signals also informed for fluvastatin, pravastatin, rosuvastatin, and simvastatin. For pitavastatin, the newest statin, middle insomnia is not studied individually or reported in SPCs; the signal obtained is positive with specificity and sensitivity.

The only statin without a positive signal of insomnia was lovastatin. This result is following a former clinical 5-year follow-up study where insomnia had a very low presence [28], but there is no other evidence found for the last 10 years about that.

The same situation of no recent evidence remains for all the rest of the statins, except for rosuvastatin information derived from the randomized controlled trial JUPITER, where the authors recommended monitoring patients on intensive therapy and performing adverse events trials for lipid-lowering agents [27].

In addition, simvastatin showed an elevated number of pairs of ADR-statin with 1210 events reported in the present research (see Appendix 2). This ADR is stated as very rare in their SPCs.

It would be interesting to dispose of a follow-up study to update the effect of insomnia with statins, special, lovastatin, and pitavastatin. If these last ones offer less generation of insomnia, they can be candidates for people—in special, the elderly—with sleep disorders.

4.1.2 Depression

In the present analysis, there is a clear positive signal of simvastatin and major depression and less sensitivity but also positive for depressed mood and depressive symptoms. In SPCs, depression is reported as ADR with unknown frequency.

Initially, the relationship between depression and metabolic disturbance, such as dyslipidemia, seems not to be clear. It has been observed that the increased appetite—in the context of a depressive episode—was the only symptom that was associated with metabolic (and inflammatory) markers [29]. The authors of this study considered that it could be a key feature of an immunometabolic form of depression.

In this sense, it looks like inadequate nutrition leading to higher levels of cholesterol can be derived from some types of depression. On the other hand, using a genetic-based approach, it showed an increased risk of depression during statin [25].

Besides, some authors analyzed the association between statin treatment and antidepressant use, and they conclude that it is unspecific (equivalent association between statins and most other drugs) and that the association between statin use and depression diagnoses is mediated by residual confounding, bias, or by downstream effects of the statin prescription (seeing a physician more often) [30].

4.1.3 Memory impairment: dementia

Owing to the widespread use of statins, the severity of cognitive dysfunction, and its high prevalence in older people, some authors reflected that the patient

communications about possible cognitive impairment must be considered and evaluated appropriately, including after discontinuation of the statin [31].

In the present research, positive signals are observed about dementia, dementia Alzheimer's type, and memory impairment for atorvastatin and rosuvastatin, as well as amnesia for atorvastatin.

Some authors considered that much of the evidence supporting statins in the prevention of dementia and Alzheimer's disease are in persons exposed to statins at mid-life as opposed to late life [32]. They conclude that statins have an evident protective effect on cognition, related to the prevention of stroke and possible subsequent vascular dementia and preventing microvascular infarcts that lead to dementia without an acute stroke, and this idea is supported by others [32–34]. Other studies have demonstrated that the overall rate of cognitive decline was not different in statin users compared with never users [35]. Nevertheless, the American Academy of Neurology does not address statin use to prevent dementia [36].

Some studies are more skeptical, with good evidence that statins given in late life to people at risk of vascular disease do not prevent cognitive decline or dementia [37]. Vascular dementia is the second commonest cause of this condition, and the authors consider a biologically plausible influence of the role in cholesterol associated with dementia. There is evidence of both the statin and nonstatin lipid-lowering drugs that were strongly associated with acute memory loss in the first 30 days following exposure in users compared with nonusers but not when compared with each other [38].

There is a conflict to determine if the balance of effects of lipids and lipid-lowering therapy falls on the branch of preventing or treating dementia or generating more risk [39].

The condition of amnesia with atorvastatin deserves a separate mention. In the present study, a positive signal only for atorvastatin was obtained (1360 cases notified). It was stated as low frequent in the factsheets, and there is no recent publication found in humans about that.

4.1.4 Dreams disorders: nightmares

A growing body of evidence indicates that statins may have potentially negative effects on nervous-system-associated diseases, including myopathies, peripheral neuropathy, intracerebral hemorrhage, cognitive impairment, depression, sleep disorders, nightmares, hallucinations, and headache [40, 41].

In a case report of atorvastatin, the authors hypothesized that the nightmares could be a direct effect of the statin on the central nervous system; they did not know if it was due to a pharmacokinetic (CYP3A4) or pharmacodynamic interaction. However, they recommend that if nightmares appear, it could be easy to avoid stopping statins [42].

Dreams disorders, not a severe condition, could lead to aversion and loss of adherence to the treatment. In the present study, pravastatin and simvastatin presented positive signals for nightmares and abnormal dreams, and fluvastatin only for nightmares. Rosuvastatin showed a positive signal with high sensitivity for daydreaming. Nightmares are reported in SPCs of all the statins with signals. On the contrary, daydreaming is not reported and could be especially compromising in older people with cognitive or mobility dysfunction.

A follow-up study of these symptoms can lead to prescribing statins less related to dream disorders ADR as atorvastatin, lovastatin, and pitavastatin.

4.2 Other positive signals related to mental disorders are mainly absent as ADRs in SPCs

4.2.1 Anxiety

It is striking that no one of these positive signals detected are reported in SPCs. As an example of contrast, cerivastatin showed an elevated number of reports [2, 43] of signals as anxiety or emotional disorder never stated in factsheets. Atorvastatin also showed an emotional distress signal.

A diagnosis of hyperlipidemia and the beginning of statin treatment could lead to anxiety about high cholesterol and its consequences. However, it is difficult to identify which anxiety is due to the onset of the treatment and associated with the fear of cardiovascular health, and which one is associated with a real ADR by statins.

In general, there is conflicting evidence of a relationship between statins and mood [44]. Some authors associate anxiety with an increased likelihood of discontinuation with statins [45]. In some groups of patients with head and neck cancer, preexisting hyperlipidemia was associated with an increased risk of new-onset anxiety/depression [46].

However, avoiding the diagnosis of the illness and chronic treatment, uncertainties about the pharmacological mechanisms, risks to health, side effects, costs, and skepticism are considered barriers to the uptake of statins [47].

The association between anxiety and nonadherence to preventive therapies remains unclear, and some authors have investigated whether the somatic symptoms of anxiety predict statin nonadherence [48].

4.2.2 Bipolar disorders

Bipolar disorder signals only appeared with rosuvastatin.

It has been observed that the continued use of drugs such as low-dose aspirin, statins, and angiotensin agents was associated with decreased rates of incident mania/bipolar disorder on both the outcome measures [49]. At least, as treatment, statins do not seem to exacerbate this cognitive dysfunction [50].

In patients with central nervous system metabolic disorders, it was hypothesized that statins may act as unmasking agents for latent neuromuscular disorders, as reported in cases of acute ataxia coincident with statin onset in individuals with bipolar disorder [51].

4.2.3 Psychiatric symptoms and psychotic disorder

It has an idea of the relation between the use of statins and preexisting psychotic disorders. The first meta-analyses published about that clarified that adjunctive therapy with statins could improve psychiatric symptoms, either negative symptoms or positive symptoms [52].

Data from the Norwegian spontaneous reporting system and from WHO's, an international database covering the period of 1988–1995, include reports of adverse drug reactions relating to psychiatric disorders (15% of the reactions to statins in the Norwegian database). Reactions include aggression, nervousness, depression, anxiety, sleeping disorders, and impotence. The pharmacological mechanisms are not elucidated but may be an effect of falling serum cholesterol [53].

Another option is that statins show a strong association with inflammatory processes that may occur due to the disorder. This condition may cause increased inflammatory markers and concurrent psychiatric symptoms. Other factors such as gender, metabolic problems, or smoking can be associated with this increase in inflammatory markers [54].

This observation could be useful to elucidate the best statin for patients with different mental disorders. In the present study, psychiatric symptoms only appeared with simvastatin and psychotic disorder with simvastatin and lovastatin.

On the other hand, fluvastatin, pitavastatin, and pravastatin have no signals.

Some studies are in favor of statins used in combination with conventional psychotropic medications for various psychiatric disorders including depression, schizophrenia, and dementia [55].

4.2.4 Suicide

Atorvastatin, lovastatin, and simvastatin showed a signal of completed suicide (290 cases for atorvastatin and 283 for simvastatin). Simvastatin also presented signals for suicidal behavior, suicidal ideation (also rosuvastatin), and suicide attempt. It appears that statin, in particular, simvastatin, is a clear candidate for studying of suicidal conditions.

There are cases with simvastatin (various doses), atorvastatin (various doses), and lovastatin that reported mood/behavior change (violent ideation, irritability, depression, and suicide) that commenced following statin initiation and persisted or progressed with continued use. Problems resolved with drug discontinuation and recurred with rechallenge were attempted [56].

Aggressive reactions associated with statins are poorly documented in the literature, but they can have a significant personal impact on a patient. The observation that other lipid-lowering agents have similar adverse effects supports the hypothesis that decreased brain cell membrane cholesterol may be important in the etiology of this psychiatric reaction [57].

4.3 Limitations of the study

The download of information on adverse drug reactions was carried out shortly before December 1, 2019, the date considered to be the start of the international pandemic by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Analyzing data before this date has the advantage of avoiding the potential and unknown interactions of the coronavirus or subsequent vaccines with pharmacological treatments.

It is known that the values of specificity and sensitivity are typically low with BCPNN methodology [23]. Nonetheless, it is acceptable with very high specificity and a low but conservative sensitivity as detected for typical positive signals for cerivastatin and other statins.

5. Conclusions

Mental disorders detected and proposed in the present study to further investigation are insomnia for pitavastatin, pravastatin, and simvastatin; dementia for

atorvastatin and rosuvastatin; and suicide and psychotic disorders for atorvastatin, lovastatin, pravastatin, rosuvastatin, and simvastatin.

Moreover, signals of central disorders as an affectation of senses for pitavastatin (hearing loss), pravastatin (visual impairment), atorvastatin (blindness), and simvastatin (ageusia) can act as confounding symptoms of mental disorders, and they would be interesting to analyze in clinical trials as early symptoms for statin interchange.

Surrendering to the low positive signals detected, fluvastatin, stands out as a candidate to contrast with the others.

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Conflict of interest

The author declares no conflict of interest.

A. Appendix 1. Details of the algorithm performed

In this analysis, the algorithm was performed with the following arguments: value of the relative risk (RR) proven to be higher than 1 (RR < 1); minimum number of cases per pair (drug-adverse reaction) to be potentially considered as a signal (N = 1); rule of decision for the generation of signals: false discovery rate (FDR); limit or threshold for the decision rule: FDR > 0.05; statistics used for ordering the drug-ADR pairs: posterior probability of the null hypothesis (post.H0); and calculation of the distribution of the statistic of interest: by approximation to the normal distribution [1a, 2a] and using empirical estimation through Monte Carlo simulations (NB. MC = 10,000) [3a]. The estimator of FDR < 0.05 and specificity (Sp) ≥ 0.99 are considered to interpret the results. Sensitivity (Se) values are typically low in the BCPNN approach [4a], Se ≥ 0.20 is considered as reference.

The estimator FDR assures that at least 95% of the signals detected are positive (only 5% of false positives). Moreover, if the estimator of false negative rate (FNR) is 50% or lower, it implicates that, at least, half of the signals rejected are effectively negative. In the results presented, all the FNRs were lower than 49%.

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B. Appendix 2. Detailed results of positive signals (FDR < 0.05; Specificity ≥ 0.99) of mental disorders related with statins reported as adverse drug reaction (ADR) in Vigiaccess™ database and analyzed by a contrasted approach of Bayesian confidence propagation neural network (BCPNN) extended to the multiple comparison setting for active ingredients groups

Interpretation of items: drug code: active ingredient reported; event effect: ADR reported; count: number of couples 'active ingredient-ADR' reported; post.H0: posterior probability of null hypothesis; FDR: false discovery rate; FNR: false negative rate; Se: Sensitivity (* ≥ 0.20); Sp: Specificity.

Insomnia; middle insomnia; terminal insomnia; sleep disorder; poor quality sleep.

Drug code	Event effect	Count	post.H0	FDR	FNR	Se	Sp
Fluvastatin	Insomnia	206	0.000	0.000	0.482	0.025	1
Pitavastatin	Insomnia	136	0.000	0.000	0.484	0.019	1
Pravastatin	Insomnia	377	0.000	0.000	0.471	0.066	1
Simvastatin	Insomnia	1210	0.039	0.008	0.450	0.144	1
Atorvastatin	Middle insomnia	92	0.160	0.049	0.421	*0.248	0.988
Pitavastatin	Middle insomnia	6	0.010	0.025	0.435	*0.197	0.995
Pravastatin	Poor quality sleep	15	0.084	0.020	0.439	0.184	0.996
Simvastatin	Poor quality sleep	45	0.090	0.021	0.438	0.188	0.996
Fluvastatin	Sleep disorder	44	0.029	0.005	0.453	0.133	0.999
Pravastatin	Sleep disorder	126	0.000	0.000	0.480	0.036	1
Simvastatin	Sleep disorder	363	0.000	0.000	0.475	0.050	1
Pitavastatin	Terminal insomnia	4	0.006	0.001	0.464	0.094	1

Depression; major depression; depressed mood; depressive symptoms.

Drug code	Event effect	Count	post.H0	FDR	FNR	Se	Sp
Rosuvastatin	Depressed mood	126	0.000	0.000	0.472	0.064	1
Simvastatin	Depressed mood	107	0.050	0.010	0.447	0.155	0.998
Cerivastatin	Depression	876	0.000	0.000	0.488	0.002	1
Simvastatin	Depressive symptom	10	0.024	0.004	0.455	0.126	0.999
Lovastatin	Major depression	7	0.039	0.008	0.450	0.144	0.999
Simvastatin	Major depression	18	0.114	0.030	0.432	*0.209	0.994

Amnesia; dementia; dementia Alzheimer's type; memory impairment.

Drug code	Event effect	Count	post.H0	FDR	FNR	Se	Sp
Atorvastatin	Amnesia	1360	0.000	0.000	0.486	0.010	1
Atorvastatin	Dementia	143	0.003	0.000	0.467	0.082	1

Drug code	Event effect	Count	post.H0	FDR	FNR	Se	Sp
Rosuvastatin	Dementia	92	0.010	0.000	0.470	0.071	1
Atorvastatin	Dementia Alzheimer's type	106	0.000	0.000	0.474	0.057	1
Rosuvastatin	Dementia Alzheimer's type	53	0.030	0.006	0.453	0.134	0.999
Atorvastatin	Memory impairment	913	0.000	0.000	0.480	0.034	1
Rosuvastatin	Memory impairment	537	0.000	0.000	0.476	0.048	1

Dreams disorders: nightmares; abnormal dreams, daydreaming.

drug code	event effect	count	post.H0	FDR	FNR	Se	Sp
Pravastatin	Abnormal dreams	34	0.057	0.012	0.445	0.161	0.998
Simvastatin	Abnormal dreams	111	0.035	0.007	0.451	0.140	0.999
Rosuvastatin	Daydreaming	5	0.100	0.025	0.435	*0.197	0.995
Fluvastatin	Nightmare	40	0.015	0.002	0.458	0.114	1
Pravastatin	Nightmare	105	0.000	0.000	0.476	0.047	1
Simvastatin	Nightmare	387	0.000	0.000	0.484	0.017	1

C. Appendix 3. Detailed results of positive signals (FDR < 0.05; Specificity ≥ 0.99) of other mental and central disorders not stated in SPCs related to statins reported as ADR in Vigiaccess™ database and analyzed by a contrasted approach of Bayesian confidence propagation neural network (BCPNN) extended to the multiple comparison setting for active ingredients groups

Interpretation of items: drug code: active ingredient reported; event effect: ADR reported; count: number of couples 'active ingredient-ADR' reported; expected count: couples 'active ingredient-ADR' expected; post.H0: posterior probability of null hypothesis; n11/E: ratio between the count observed and the count expected of the corresponding couple; drug margin: number of reports of a drug; event margin: number of reports of an event; FDR: false discovery rate; FNR: false negative rate; Se: Sensitivity (* ≥ 0.20); Sp: Specificity.

Loss of special senses not reported in SPCs: blindness, unilateral blindness, deafness, unilateral deafness, anosmia, ageusia, balance disorder.

Drug code	Event effect	Count	post.H0	FDR	FNR	Se	Sp
Lovastatin	Ageusia	44	0.000	0.000	0.481	0.028	1
Pravastatin	Ageusia	29	0.043	0.008	0.449	0.148	0.999
Simvastatin	Ageusia	85	0.124	0.034	0.430	*0.217	0.993
Pravastatin	Anosmia	11	0.044	0.009	0.449	0.148	0.999
Atorvastatin	Balance disorder	468	0.034	0.007	0.451	0.139	0.999
Simvastatin	Balance disorder	289	0.014	0.002	0.459	0.111	1
Atorvastatin	Blindness	169	0.000	0.000	0.473	0.059	1

Drug code	Event effect	Count	post.H0	FDR	FNR	Se	Sp
Lovastatin	Blindness	28	0.003	0.000	0.466	0.086	1
Atorvastatin	Blindness unilateral	56	0.045	0.009	0.449	0.149	1
Rosuvastatin	Blindness unilateral	33	0.084	0.020	0.439	0.184	0.996
Atorvastatin	Deafness	215	0.000	0.000	0.480	0.034	1
Lovastatin	Deafness	32	0.002	0.000	0.468	0.079	1
Atorvastatin	Deafness unilateral	37	0.041	0.008	0.449	0.146	0.999
Rosuvastatin	Deafness unilateral	21	0.109	0.028	0.433	*0.203	0.994
Pravastatin	Diplopia	84	0.000	0.000	0.485	0.015	1
Lovastatin	Diplopia	39	0.002	0.000	0.468	0.078	1
Lovastatin	Visual impairment	367	0.000	0.000	0.488	0.003	1
Pravastatin	Visual impairment	139	0.021	0.004	0.456	0.123	1
Rosuvastatin	Visual acuity reduced	91	0.000	0.000	0.479	0.038	1
Pravastatin	Vision blurred	146	0.000	0.000	0.479	0.038	1
Atorvastatin	Vision blurred	617	0.124	0.034	0.429	*0.218	0.992
Pravastatin	Sudden hearing loss	5	0.029	0.005	0.453	0.133	0.999
Pitavastatin	Sudden hearing loss	2	0.148	0.043	0.424	*0.237	0.990
Atorvastatin	Tinnitus	511	0.000	0.000	0.477	0.0435	1
Pravastatin	Tinnitus	81	0.034	0.006	0.452	0.138	0.999
Pravastatin	Dysgeusia	110	0.000	0.000	0.482	0.026	1
Lovastatin	Dysgeusia	67	0.006	0.001	0.464	0.093	1

Other mental health problems not stated in SPCs: anxiety, bipolar disorder, psychiatric symptom, psychotic disorder, emotional disorder, emotional distress.

Drug code	Event effect	Count	post.H0	FDR	FNR	Se	Sp
cerivastatin	Anxiety	2767	0	0.000	0.489	0.010	1
rosuvastatin	Bipolar disorder	33	0.000	0.000	0.472	0.066	1
rosuvastatin	Bipolar I disorder	5	0.066	0.014	0.444	0.169	0.998
cerivastatin	Emotional disorder	53	0.000	0.000	0.485	0.016	1
atorvastatin	Emotional distress	337	0.007	0.001	0.464	0.096	1
cerivastatin	Emotional distress	391	0.000	0.000	0.488	0.002	1
simvastatin	Psychiatric symptom	32	0.000	0.000	0.478	0.042	1
lovastatin	Psychotic disorder	12	0.0047	0.001	0.466	0.089	1
simvastatin	Psychotic disorder	34	0.011	0.002	0.461	0.106	1

Suicide not stated in SPCs: complete suicide, suicide attempt, suicidal ideation, suicidal behavior.

Drug code	Event effect	Count	post.H0	FDR	FNR	Se	Sp
Atorvastatin	Completed suicide	290	0.025	0.004	0.455	0.128	1
Lovastatin	Completed suicide	50	0.004	0.001	0.465	0.090	1

Drug code	Event effect	Count	post.H0	FDR	FNR	Se	Sp
Simvastatin	Completed suicide	283	0.000	0.000	0.485	0.014	1
Simvastatin	Suicidal behavior	6	0.093	0.022	0.437	0.191	0.996
Rosuvastatin	Suicidal ideation	94	0.030	0.006	0.453	0.134	0.999
Simvastatin	Suicidal ideation	91	0.063	0.014	0.444	0.166	0.998
Simvastatin	Suicide attempt	97	0.000	0.000	0.483	0.022	1

D. Appendix 4. Detailed results of positive signals (FDR < 0.05; Specificity ≥ 0.99) of disorders referred in main manuscript related to statins reported as ADR in Vigiaccess™ database and analyzed by a contrasted approach of Bayesian confidence propagation neural network (BCPNN) extended to the multiple comparison setting for active ingredients groups

Interpretation of items: drug code: active ingredient reported; event effect: ADR reported; count: number of couples 'active ingredient-ADR' reported; expected count: couples 'active ingredient-ADR' expected; post.H0: posterior probability of null hypothesis; n11/E: ratio between the count observed and the count expected of the corresponding couple; drug margin: number of reports of a drug; event margin: number of reports of an event; FDR: false discovery rate; FNR: false negative rate; Se: Sensitivity(* ≥ 0.20); Sp: Specificity.

Rhabdomyolysis.

Drug code	Event effect	Count	post.H0	FDR	FNR	Se	Sp
Cerivastatin	Rhabdomyolysis	5219	0	0.000	0.488	0.001	1
Simvastatin	Rhabdomyolysis	4873	0.000	0.000	0.487	0.004	1

Transaminases increased.

Drug code	Event effect	Count	post.H0	FDR	FNR	Se	Sp
Fluvastatin	Transaminases increased	128	0.000	0.000	0.487	0.010	1
Atorvastatin	Transaminases increased	787	0.000	0.000	0.477	0.048	1
Simvastatin	Transaminases increased	467	0.000	0.000	0.474	0.059	1

Myalgia.

Drug code	Event effect	Count	post.H0	FDR	FNR	Se	Sp
Simvastatin	Myalgia	11,860	0.000	0.000	0.487	0.005	1
Fluvastatin	Myalgia	1588	0.000	0.000	0.487	0.007	1
Pravastatin	Myalgia	3209	0.000	0.000	0.485	0.014	1
Lovastatin	Myalgia	2278	0.071	0.016	0.442	0.174	0.997

Myopathy.

Drug code	Event effect	Count	post.H0	FDR	FNR	Se	Sp
Lovastatin	Myopathy	499	0.000	0.000	0.487	0.006	1

Drug code	Event effect	Count	post.H0	FDR	FNR	Se	Sp
Cerivastatin	Myopathy	566	0.000	0.000	0.486	0.010	1
Simvastatin	Myopathy	1327	0.000	0.000	0.485	0.014	1
Fluvastatin	Myopathy	171	0.000	0.000	0.479	0.035	1

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Chapter 8

Signum Espial

Favour Osisanwo

Abstract

The objective of pharmacovigilance is to guarantee the arrangement of early admonitions concerning any obscure antagonistic impact of the medication to guarantee patients' security, safeguard the drug brand name and simplicity of administrative consistence. Since clinical preliminaries are restricted by various things in their disclosure of antagonistic medication response corresponding to the new restorative item, signal administration is locked in to guarantee that essential data are obtained with regard to medication. Signal espial is a piece in the master plan of signal management, a significant stage in pharmacovigilance. This exposition expects to discuss the subtleties engaged with antagonistic response drug location risk up to its approval and assessment process. Signals are obtained from various sources that are distinguished by different legitimate associations. They are focused on in light of a rule of classification, which is then assessed and prompts one more part of pharmacovigilance risk, the board which is outside the extent of this review.

Keywords: signal, adverse reactions, medicinal product, pharmacovigilance, signal management

1. Introduction

Signum Espial is a piece of the means embraced in pharmacovigilance. Signum is the Latin name for signal while Espial is known as detection or recognition. Signal detection is the arrangement of exercises performed to decide whether there are new dangers related to the restorative item or the gamble has changed. Presently, the signal is used to manage revealed conceivable causal relationship of a medication according to an unfavorable occasion, which might be muddled in totally archived during the pre-showcasing stage. A speculative circumstance should be approved or objected. It is significantly engaged with the post-marketing stage, used to collect extra data about the antagonistic or gainful impacts of intercession of medication or definitely known data about the relationship of the medication with an unfriendly medication impact. Signum Espial, otherwise called signal detection, is the demonstration of looking and recognizing signals utilizing occasion information from requested sources, spontaneous obtained, and legally binding agreement or administrative specialists, which are examined and dissected to distinguish designs that show new wellbeing data or new data changes benefit-hazard proportion related with the utilization of the restorative item. These signs

could be created from subjective examination or quantitative investigation, that is to say, through information mining. The quantity of reports required for exact analysis is not entirely set in stone because of the nature of the impact, nature of the report, and conceivable proof of different sources of various medications. This interaction is needed for a powerful gamble/benefit assessment of medications. It is likewise expected to distinguish possible dangers and ways the dangers can be overseen, which safeguards the organization's picture and gives purchasers further developed drugs. There are a few stages to elaborate, which would be discussed further in the chapter.

Pharmacovigilance, as stated earlier, is the process of monitoring adverse drug reactions and adverse drug events, detecting previously unidentified or an insufficiently understood hazardous medicinal response, which could not have been seen throughout the drug trials lifecycle, and also tracking trend in consumers' sentiment regarding the medicinal product [1]. Various methods are undertaken to ensure the collation of data needed for adequate analysis. It could be collected through passive surveillance, active surveillance, cohort event monitoring, and targeted clinical investigations [1]. The data generated during clinical trials, before the dispensation of the drugs to the market, are not enough to know all risks involved in the drug usage [2]. A signal is the possible link between a potential or established baneful drug reaction and the drug itself; which was previously known or not properly validated.

2. Signal exposition

Before we dive into the process of signal management, it is essential we understand a few terminologies. Starting with the most basic of all: signal.

A *signal*, according to WHO, is reported information on a possible causal between an adverse effect and a drug, the relationship being unclear or incompletely documented previously. It is important to note that a signal is not a verified opinion but a hypothesis-generating situation that must be validated [3].

2.1 Sources of signals

There are different sources from where adverse drug reports and dangerous event reports can be obtained. These sources can be classified into *Unsolicited Sources and Solicited sources.*

2.1.1 Unsolicited sources

These are reports not asked for, that is, not intentionally requested by a person and it is produced from them without their permission. These sources are spontaneous reports, literature sources, and the media (**Figure 1**).

2.1.2 Solicited sources

These are reports deduced from organized data collections such as clinical trials and post-marketing studies, patient support programs, and drug regulatory authority and pharmaceutical companies (**Figure 2**).

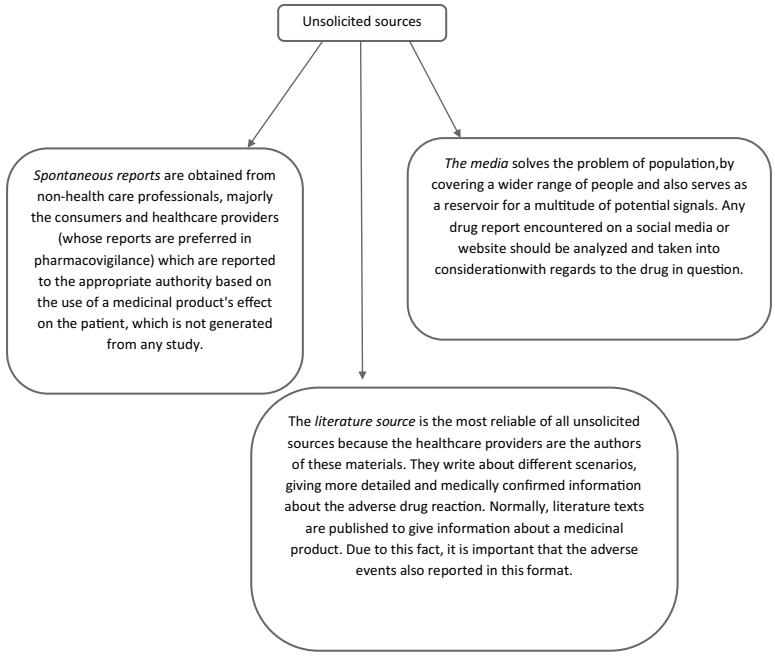

Figure 1.
The different unsolicited sources.

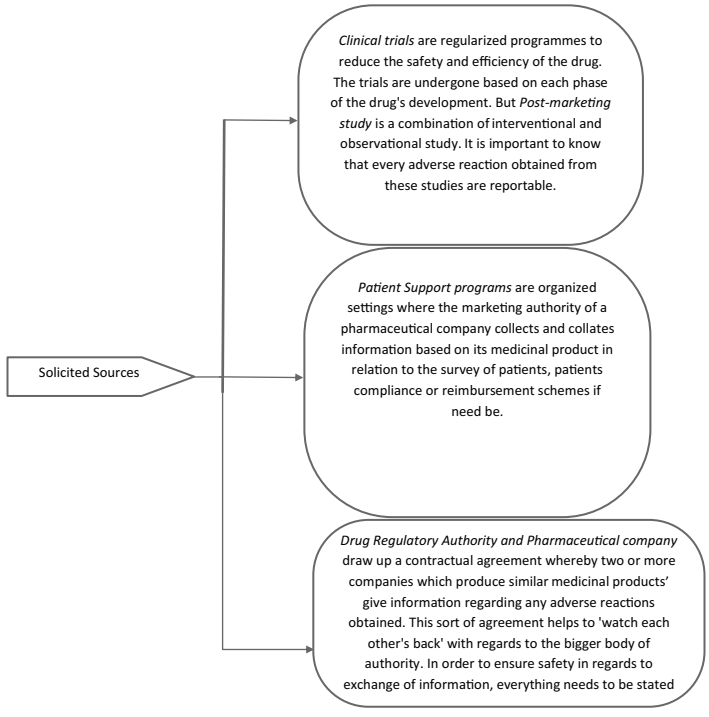

Figure 2.
The various solicited sources.

3. Signal management

It refers to a series of activities undergone to determine whether there are other threats regarding a medical product or if the risks earlier discovered had changed. The process ranges from detection to validation and evaluation.

3.1 Signal detection

Signal detection is the act of searching for and identifying signals, as explained earlier, possible information regarding a drug and a dangerous reaction using event data from any source. It is the method of recognizing the linkage between a drug and an adverse event. It is faster in the collation process when the number of drug users is more in relation to the saying, "the more the merrier." Also, the frequency of the adverse reaction and the rate of reports to the appropriate quarters aids in its detection [3].

3.1.1 Importance of signal detection

- It is the most important objective of pharmacovigilance.
- Early discovery of signals helps to seek out potential risks in relation to the marketed drug.
- When discovered risks about the medicinal product are validated, it helps the pharmaceutical company to produce improved drugs for patients.
- This protects the brand name of the pharmaceutical company as early signal detection leads to an early risk management strategy.
- It is part of the legal obligation of the company to run a continuous risk profile about its marketed drug.

3.1.2 Methods of signal detection

There are various ways by which signals are detected. It should be through the traditional means or data mining algorithms. It could be through individual case reviews, aggregate analysis, or periodic reports. It could also be through disproportional reporting ratio or multi-item gamma poison shrinker [2].

3.2 Signal validation

This is a process in which collated data concerning a detected signal is evaluated to ensure their verification. In accordance with Article 21(1) of the Commission Implementing Regulation (EU) No 520/212, the approval of signs depends on the assessment of the information supporting the distinguished sign. The goal of this evaluation is to confirm whether the surveyed documentation contains adequate proof showing the expected presence of another causal affiliation (or of another part of a known relationship) between the thought therapeutic item and the unfavorable response, and consequently legitimizes further examination of the sign. The item data, PSUR, and risk management plan (RMP) ought to be considered to check the oddity of the affiliation. This assessment is mostly established on the survey of line

postings or of individual case safety report (ICSR) frames yet, it tends to be supplemented by the investigation of confirmations given in the logical and clinical writing. It ought to be underlined that the survey of line postings and ICSR structures means to decide whether, in light of their general assessment, the sign is approved and should be conveyed to the PRAC rapporteur. This assessment ought to be founded on clinical judgment and may require some level of causality appraisal of the cases [4].

The sign approval action is characterized in Article 19(1) of the Commission Implementing Regulation (EU) No 520/212, and compares to "the most common way of assessing the information supporting the distinguished signal to check that the accessible documentation contains adequate proof exhibiting the presence of another possibly causal affiliation or another part of a known affiliation, and consequently legitimizes further examination of the signal." The idea of signal approval requires the assessment of all the data accessible in the cases to decide if a case series, less oftentimes one single case which has raised consideration, can be viewed as an approved signal.

When this progression has been finished, the signal can either be

- approved and submitted to the PRAC rapporteur for affirmation,
- discredited and shut, and
- checked.

The accompanying components ought to be thought about (as introduced in the request for prioritization for every component) to decide if a sign can be viewed as substantial and therefore shipped off to the PRAC (Pharmacovigilance Risk Assessment Committees) rapporteur for affirmation. In the evaluation of regarding detected signal, these criteria must be checked and marked; strength of the signal, clinical references, and the originality of the signal.

3.2.1 Strength of signal

There is a conceivable worldly relationship in most of the cases with a viable order in the event of the antagonistic response (counting first signs or side effects) and the organization of the thought therapeutic item. An adequate number of the cases (without data on dechallenge or rechallenge results) does not present confounders or hazard factors like simultaneous circumstances/comorbidities, co-drugs, patients' clinical chronicles, or socioeconomics. The number of strong cases ought to be thought of as along with.

- the total patients' openness for the said therapeutic item (in light of the information from the latest PSUR), and.
- the disproportionality of revealing the unfavorable response.

The signal should be identified from imperative discoveries announced in requested or unconstrained cases or distributed in logical and clinical writing. Also, a portion relationship should be noticed in a few of the detailed cases. Some consistency ought to be seen in the detailed cases with respect to the example of side effects and accessible wellsprings of proof.

There must be a causal pharmacological, natural, or pharmacokinetic interface between the unfriendly response and the organization of the thought therapeutic item. The detailed signs, side effects, and the performed tests should be viable with the clinical definitions and practices.

3.2.2 Clinical references

Is the adverse response perilous, or does it require patient hospitalization with clinical intercessions (for example blood transfusion), or is there a high extent of announced fatalities or inabilities, which cannot be connected to the normal advancement of the treated illness or to the patient's comorbidities? It is vital that these inquiries are considered for the clinical aspect. Does the adverse, unfavorable response happen in weak populace subgroups (for example pregnant ladies, kids, or old) or in patients with prior risk factors (for example liver or heart illnesses)? Does the thought unfriendly response create in a setting of medication cooperation, word-related openness, quality issue, fake medication, or it happen in specific examples of purpose (for example, drug blunders, off-name use, glut, misuse, and abuse)?

It is important to consider whether the thought unfavorable response could affect general well-being or the public view of the security of the thought restorative item. In certain circumstances, the clinical meaning of the unfriendly response might influence the gamble benefit profile of the thought restorative item, and as a result, atrocities might be expected to limit the gamble. In different occurrences, the thought unfavorable response might be preventable or measures could be set up to deal with the gamble. The effect on the treated sickness of the activities imagined to relieve the new gamble and the accessibility of elective therapies ought to be thought about while surveying the clinical pertinence of a signal [4].

3.2.3 Originality of signal

Considering the newness of the sign is a critical activity in assessing the sign. A couple of clinical or non-clinical tantamount revelations were seen during the progression of the examined remedial thing. This movement requires examining the evaluation reports of the promoting authorization application appraisal to affirm whether the issue was by then perceived in various districts of the development. The disagreeable reaction has furthermore been portrayed in huge intelligent and clinical composing related to the remedial thing, dynamic substance, or supportive aftereffects of a comparative pharmacological class [5]. The hostile reaction can be associated with a security concern, recently depicted in the EU thing information, PSUR, or other managerial methods for the restorative item. As per the guidance for signal acknowledgment of terms associated with recorded terms/referred to bets, a sign still might be endorsed, for example, to envision further bet minimization measures, on the off chance that new cases (or composing) give additional confirmation that

- shows other sincere measures (for instance deadly cases),
- shows a potential bet in the gamble the executives plan,
- further portrays a prosperity concern recently kept in the thing information, or

- Disturbs an idea on a prosperity concern as of late supported in a PSUR(Periodic Safety Update Report).

Note: After the sign has been assessed through these series of cycles, it is critical that it is reinforced further by open proof. Its affirmation is achieved by clinical writing surveys, different data sets like WHO or the maker.

3.3 Signal assessment

This comprises an intensive pharmacological, clinical, and epidemiological examination of all the data accessible with respect to the sign of interest. This appraisal is accomplished in quantitative and subjective measures [2].

Quantitative analysis

- Number of case reports with respect to the sign.
- Measurable dissimilarity and significance.

Qualitative analysis

- General presence of a specific component of an example
- Uncommonness of chat discoveries
- The dose to reaction relationship
- Then it is conveyed to time the antagonistic response.
- Site of event
- The pharmacological mechanism, that is, the pharmacokinetics and pharmacodynamics of the medication.
- The neurotic instrument of the antagonistic response
- Any medication subordinate antibodies
- Presence or nonattendance of strange metabolites
- Indicative markers
- Past involvement in related drugs
- Any occasion known to frequently be drug-actuated
- Qualities nature and goals of the unfriendly occasions.
- Exactness and legitimacy of documentation
- Case setback appraisal.

These are simple to make reference to a couple of markers required for an express evaluation. Results got from this are additionally taken for prioritization.

3.4 The signal's "scale of preference"

In a bid to approve the genuineness of a sign, it was essential to take note of the effect of the unfavorable occasion on general wellbeing, as prior expressed. It is important to speedily distinguish the signs with significant general well-being effects or that might influence the advantage risk balance of the clinical items in the treated patients. To organize the size of inclination, the strength and consistency of proof ought to be thought of.

3.4.1 Methods of getting the scale of preference

1. WHO Triage.

2. Impact analysis by Marketing Authority.

3.4.1.1 WHO Triage

As indicated by the Merriam-Webster's word reference, an emergency is the arranging and portion of treatment to patients, particularly fight and calamity casualties as per an arrangement of needs intended to amplify the number of administrations.

However, for this situation, It is the allotting of consideration regarding signals that can cause a significant effect on general well-being or hazardous consequences for managed patients. This end is gotten in view of explicit boundaries as indicated by WHO.

- Is this unfavorable occasion extreme or not?

- Was the response expected or not?

- Is the uniqueness score sheet high or not?

- Are more than one nation confronting this issue?

3.4.1.2 Impact analysis by marketing authority

This is an examined and contemplated quantitative score in light of "proof" and general well-being. For proof score; we consider the level of dissimilarity, the strength of evidence, and the biological plausibility and reasonableness.

For the general wellbeing score, we check the number of revealed cases each year, the normal wellbeing results and the detailing rate in relationship to the degree of medication openness.

3.4.2 Categorization of signal

After the analysis above is carried out on every signal obtained, they are then categorized into consideration *or not* based on the positivity or negativity of the results.

a. Refuted signals: These signals are closed out as every evaluation to validate turned out negative.

b. Unconfirmed signals: This results in the monitoring of events over time and regularly reprioritizing it based on new information if obtained. Due to this fact that the outcome of results was not solid enough to validate probably based on a lack of information for evaluation on the signal, or frequency was not enough, but they are still not strong to dispute the possibility of its existence.

c. Confirmed signal: It leads to movements of signals in the evaluation process. They are evaluated based on casualty, frequency of occurrence, clinical implications on patient's health, and preventability [2].

3.5 Decision making

Depending not the assessment results, the following decisions are taken.

- Arrangement a concentrate explicitly researching a specific sign
- Audit the advantages and dangers of items either to suspend or deny the showcasing approval or to propose a change to the item data.
- Issue an admonition to the well-being experts utilizing a formal and official expert correspondence.
- Or on the other hand, hold the issue under audit
- It might likewise happen that the sign was not genuine and the issue can be retired.

4. Conclusion

In summary, signal espial is a very crucial strong in pharmacovigilance. Since its main aim is drug safety, if adequate information is obtained about each signal gotten, effectiveness in pharmacovigilance is well on being achieved. The signal management process has just shown how extensive research is done concerning adverse events. Just to add that it is important to put the advice of the marketing authority into consideration as an extensive assessment has been undertaken regarding each signal. From its detection down to its evaluation and then prioritization, we are ensured of better wellness regarding each medical product released to the market.

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Conflict of interest

"The authors declare no conflict of interest."

Appendices and nomenclature

EU	European Union
ICSR	Individual Case Safety Report
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
RMP	Risk Management Plan
WHO	World Health Organization

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This book discusses various topics in pharmacovigilance. The first section addresses such topics as approaches to minimize adverse drug reactions, different stakeholders and their importance in pharmaceutical policy development, changing needs for pharmacovigilance in the African region, machine learning applications in pharmacovigilance, and pharmacovigilance of biological drugs. The second section discusses signal detection, which is a promising approach that helps in the early identification of new, rare drug reactions (desired or undesired).

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