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Scope of Pharmacovigilance: Comprehensive Review

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Pharmacovigilance aims to preserve general health by identifying, evaluating, and minimizing health issues to ensure that the benefits of accessible treatments outweigh the potential risks. However, the retraction (withdrawal) of specific medications from global markets has increasingly focused on pharmacovigilance approaches, raised concerns about improvements to the current pharmacovigilance system, and highlighted the need to ensure uniformity among international guidelines governing the detailing of side effects ("Adverse Drug Reactions" - A.D.R.s).
Concerns with the nature and safety of drugs as noted by medication guidelines. A sound medication policy is required to ensure the safety, viability, and nature of pharmaceuticals as well as the accuracy and applicability of the medication information made available to the general public. Medication guidelines cover a wide range of functions, including authorizing, reviewing manufacturing facilities and distribution channels, item evaluation and enrollment, observing adverse drug reactions (ADR), controlling medication advancement and publicizing, and controlling clinical medication preliminary studies.

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1. INTRODUCTION

The prescribed medication has enormous advantages for humanity & results in a considerable decrease in mortality & morbidity. Be that as it may, despite the fact that they are by and large seen as having useful impacts, medications (counting excipients like preservatives, flavoring agents, additives, and so forth), have the possibility of creating undesirable or adverse effects regardless of how capably they are utilized [1].

With the expanding utilization of meds for the treatment and prophylaxis of diseases, monitoring for adverse drug reactions (A.D.R.s) is a necessary and growing need; regardless of the reality that most adverse drug reactions (A.D.R.s) can be prevented, it still standing as one of the top ten leading causes of death in certain nations [2]. Moreover, appropriate services to treat adverse drug events (A.D.R.s) force a high monetary load on medical services. Along these lines vital to constitute a pharmacovigilance (P.V.) framework for monitoring the expansion in the utilization of prescriptions out of consistent checking of A.D.R.s & issues linked to the use of medications for safeguarding medications safety consistently and for whole levels of the medical care framework [3].

WHO characterizes pharmacovigilance as the "science & activities regarding the discovery, appraisal, comprehension, and avoidance of horrible effects or another possible medicine-related issue" [4]. Pharmacovigilance (P.V.) are an umbrella term used to portray the cycles for checking and assessing adverse drug reactions (A.D.R.s) after restorative items are authorized [5].

Mechanisms of action of the medicines that could reduce or increase the effects of medicine in the human body. Chemistry is one of the sciences that help pharmacovigilance achieve its goals and answers some important questions: such as what is the active substance's decay time in the body? What are the effects of taking another medicine simultaneously (medicine interactions)? What is the transport phenomenon that allows substances to enter and exit organisms? Pharmacokinetics and pharmacodynamics will undoubtedly aid in answering those questions, as well as chemistry, which includes reaction rates, thermodynamic equilibrium, adsorption and desorption processes, diffusion rates, and so on.

The outcome of these complex reactions (pharmacokinetics) and transport phenomena (pharmacodynamics) within the body demonstrate the drug's effectiveness, adverse reactions, and events caused by drug quality, inappropriate therapy, unusual purposes, intoxications, and so on [6].

This methodology is a continuum all through the course of medication advancement, from introductory innovative work exercises to conclusive customer use [7,8] Fig. (1)

The pharmacovigilance framework is generally partitioned into two phases:

Pre-marketing surveillance: Adverse drug reactions (A.D.R.s) from preclinical screening and Phase I, II, and III clinical preliminaries; and

Post-marketing surveillance: Adverse drug reactions (A.D.R.s) from the post-endorsement stage and all through a medication's market life.

Evaluation of pre-marketing safety is by and large restricted for children. This ordinarily results from not many youngsters registered in pediatric clinical experiments as well as the long latency between the beginning of the response and exposition to the medication; also, uncommon adverse responses may thusly not be perceivable during this stage. The measure of devoted data on the safety of prescriptions for youths, children, & neonates at the season of advertising approval is subsequently very restricted, which stances significantly more dependence on pharmacovigilance in the post-showcasing stage [9].

The module on experiment layout includes issues about effectiveness and integrity data from Phase I to III trials, involving the inclusions of genealogically short-term follow-up in medication approval studies.

Post-marketing pharmacovigilance: can be directed through active and passive surveillance frameworks. During passive surveillance, medical experts & / or patients themselves send

unconstrained reports depicting an A.D.R. after at least one therapeutic item are sent to the marketing approval holder or regulatory authority. At times such first case reports are distributed. Gynecomastia is an H.I.V. prepubertal girl induced by efavirenz is an example of a case report published in 2013 [10]. Theories about the relationship between exposure to medication & the outcome can be generated from a series of case report. Cases of gynecomastia declared to the National H.I.V. & Tuberculosis Health Care in South Africa is another example published in 2016 [11].

Active surveillance includes upgraded or designated checking for specific events or medications and looks to discover the number of adverse drug reactions (A.D.R.) out of a prearranged procedure totally. Toxicity monitoring is also known as active surveillance [12]. As an example of active surveillance is a cohort survey that assessed the recommendation of adherence to and A.D.R. associated with A.R.T. in a huge program in Lagos, Nigeria [13].

1.1 Pharmacovigilance History (PV):

Despite the fact that pharmacovigilance is as yet at its outset, it isn't new. Pharmacovigilance began around 170 years back, despite the fact that it was not yet named as such around then. A very long-term history of numerous appalling tragedies has assumed a basic part in forming the present-day drug improvement designs and cycles, none more so than those worried about pharmacovigilance. [14,15] Several of the cases which are significant in the recorded perspective are: [16]

- Sulphanilamide elixir (1937) led to children's poisoning. It was recognized that it was a defect in the formulation, which prompted enhancements in Pharmaceutical guidelines.
- Misfortune of thalidomide (1961) where thalidomide was utilized to treat nausea in pregnant women, infants born suffering from phocomelia which is due to the use of this medication [17].
- The utilization of Practolol (1975) that led to oculomucocutaneous response perceived by U.K. specialists prompted Prescription events monitoring (P.E.M.) [16].

The worldwide arrangement of Pharmacovigilance first evolved following the thalidomide misfortune during the 1960s. Preferably, pharmacovigilance adopts a daily existence cycle strategy, centering not just on the properties of the endorsed medication yet additionally on how it is detailed, apportioned, and directed [17].

1.2 Pharmacovigilance System Objectives

- Ameliorate the care of the patient & well-being according to meds utilization.
- Ameliorate safety & public health according to meds utilization.
- Reveal issues connected with meds utilization & convey discoveries without wasting much time.
- To Contribute to the appraisal of the advantage, harm, viability, and hazard of drugs, prompting the avoidance of mischief and boost of advantages,
- Promote the safe, logical, and more efficient (inclusive of cost-effective) utilization of medication.
- An advance agreement, instruction, and clinical preparation in pharmacovigilance and its powerful correspondence to the general population [1].

1.3 Key Goals of Pharmacovigilance

(1) To promote safe, effective, and rational usage of pharmaceuticals.
(2) To promote awareness among patients and the general public regarding the rational use of medicines via effective communication.
(3) Enhance patient safety and care in relation to the use of medicines.
(4) Recognize risks related to meds utilization.
(5) Take part in comparative evaluation of potentially useful & pharmaceuticals adverse effects which aid improving nature of usage.
(6) Identify & report suspected ADRs [3].

1.4 Pharmacovigilance Scope

The extent of pharmacovigilance has grown astoundingly as of late and is presently considered to incorporate the accompanying domains (Fig. 1):

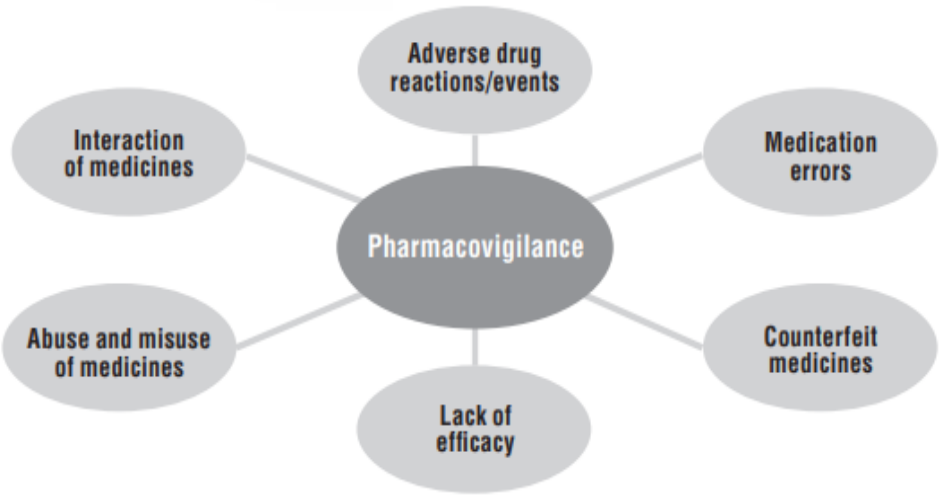

Fig. 1. Domains of Pharmacovigilance

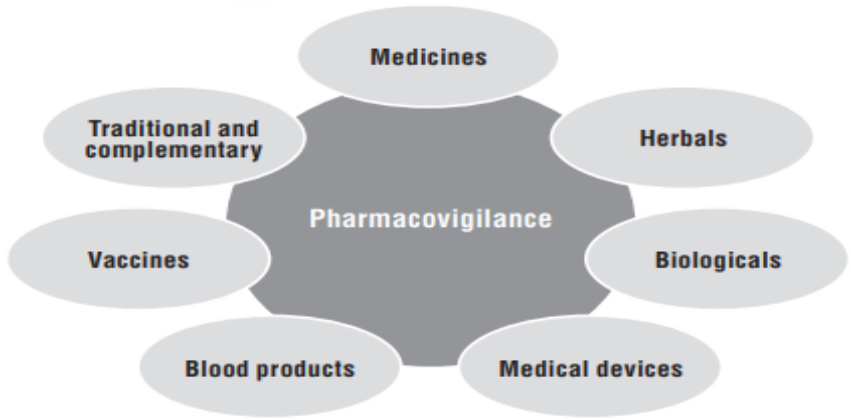

Fig. 2. Products of Pharmacovigilance

Products go past traditional medications and furthermore incorporate natural herbs, other conventional and dietary supplements, vaccines, blood products, and probably clinical gadgets (Fig. 2).

It is vital to have as a primary concern the whole extent of pharmacovigilance and the range of items considered through the development and utilization of a group of pointers to serve as tools for their assessment & observation [4,18].

1.5 Significance of Pharmacovigilance

When a new drug is presented on the market, there is still plenty of obscure things concerning the safety of this new medication. Different patients utilize these drugs for various ailments, which may be utilizing multiple different medications and should be following various practices and diets, which may unfavorably influence the effect of medication on them. Additionally, a similar medication may vary in the way of its manufacturing. Moreover, adverse drug reactions (A.D.R.s) may likewise happen when medications are brought with conventional and natural meds, which must be observed through pharmacovigilance. Now and again, adverse drug reactions (A.D.R.s) of specific medication may happen just in one nation or locale. To forestall all unjustifiable physical, mental and monetary enduring of patients, pharmacovigilance ends up being a significant observing system for medication safety in a country with the help of specialists, drug specialists, attendants, and other health experts of the country [19].

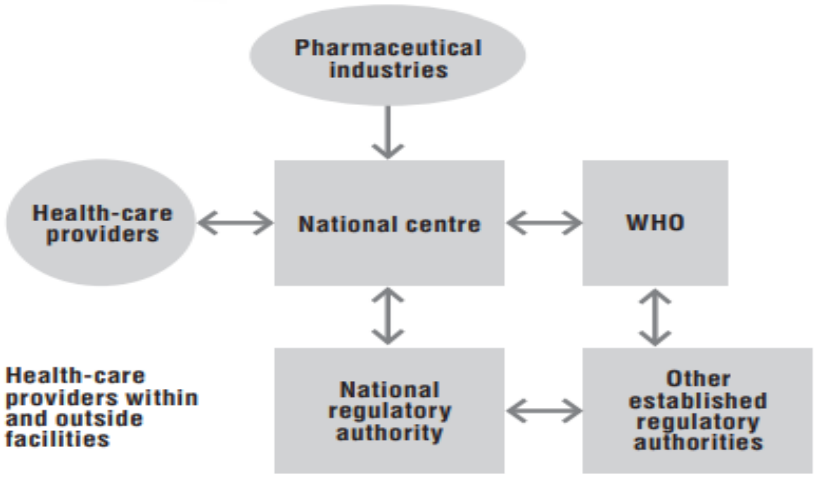

Fig. 3. Significance of Pharmacovigilance

2. ADVERSE DRUG REACTIONS (A.D.R.S)

At times, the given meds might hurt the patients at a typical dose, which are called Adverse Drug Reactions (A.D.R.) [20]. Side effect is not the same as an adverse drug reaction. The assessment of A.D.R.s is generally basic in the pharmacovigilance field.
Concerning advertised cures, a reasonable meaning of an adverse drug reaction is as per the following:

1) Unexpected/Unlisted Adverse Drug Reactions (A.D.R.s):
   An adverse drug reaction (A.D.R.s) is the nature or brutality of medication that isn't dependable with the appropriate drug information accessible at the hour of clinical trials [20].
   The organization required assistance during agents' pamphlets for an unapproved drug. A brief synopsis of the medication information sheet for an authority item.
2) Expected/Recorded Adverse Drug Reactions (A.D.R.s):
   The data about adverse drug reactions (A.D.R.s) like nature or seriousness and particularity of the medication is as of now recorded [21].

Adverse Drug Reactions (A.D.R.s) Classification:

2.1 Type A Effects

Expanded (augment) pharmacological effect: These are expected effects & it is dose-related; these effects are due to overstated pharmacological impacts. These effects (type A) are common & dose-dependent and may regularly be averted by utilizing dosages that are suitable to the singular patient.

2.2 Type B Effects

Unusual effects (idiosyncratic or Bizarre): These are unpredictable effects & it is dose unrelated (Patient responses) typically happen in just a few patients and show few or dose-independent connections. These effects (type B) are uncommon & unpredictable.

2.3 Type C Effects

These effects are chronic and refer to medication utilization, frequently for obscure reasons, expanding the recurrence of a "spontaneous" ailment. These effects (Type C) are both common & critical (like malignant) & may affect general well-being. These impacts are incidental & frequently related to prolonging haul impacts.

2.4 Type D Effects

These impacts are delay onset effects (dose unrelated) like carcinogenic effects (for example, immunosuppressant) & teratogenic effects (for example, fetal hydantoin syndrome).

2.5 Type E Effects

The effect of treatment ends.

2.6 Type F Effects

Failure of therapy [1].

3. ADVERSE DRUG REACTIONS REPORTING

At the point when the adverse response to certain medications is possibly genuine or clinically significant, all medical care laborers, including specialists, pharmacists, attendants, and other health care providers, are mentioned to illustrate it. Reporting an adverse drug reaction (A.D.R.s) to pharmacovigilance is important [22].

Spontaneous Reporting System:

a) Regionalization.
b) Repossession of additional information.
c) Admittance to immensely significant pre and post-marketing data.
d) Definite medication use information.
e) Normalized assessment of causality and importance.
f) Inducement/ Encouragement [22].

3.1 Adverse Drug Reactions (A.D.R.s) Documentation

The curriculum of pharmacovigilance passed on an overall spur that all speculated drug-related adverse effects ought to be laid out. Its reports concerned the following:

1) All the adverse reactions doubtful or happened to new medications and medications of recent concern.
2) Documentation of different medications that cause adverse drug reactions (A.D.R.s) that include death, perilous conditions, inability, hospitalization, and innate irregularities.

The critical adverse response of medications ought to be reported within a week. Other data concerning adverse reactions must be reported within eight days. The structure of A.D.R.s may be gathered out of any P.V. place. These forms are reviewed, and the information is passed forward to the regional center & from this point onward, it is pushed to the zonal center. The subtleties were measurably examined & sent to WHO-Uppsala Monitoring advisory group (U.M.C.) [22].

3.2 Adverse Drug Reactions Reporting Procedure

The principal obligation of all P.V. centers is to state whole suspicious adverse reactions related to medication utilization whenever found. These A.D.R.s' information must be reported and organized.

3.3 Monitoring of Adverse Drug Reactions (A.D.R.s)

Monitoring of A.D.R.s is a practice of consistently checking the unwanted effect of utilizing medication. Pharmacovigilance plays a basic pantomime in observing A.D.R.s.

Drug regulators intrinsically check their marketed medicinal products & enroll every presumed adverse response is distinguished. Use of different medicinal products, clinical gadgets, herbals, cosmetic products, etc. Assuming that any adverse responses are not expressed, it might bring about harmful and dangerous effects of medicinal items. In this manner, appropriately leading adverse drug reaction monitoring projects will assist with lessening the unsafe impacts of medical products [23].

Table 1. Adverse Drug Reactions Reporting Procedure

Elements in ADR reporting	Reporting Necessary	Others
What should be reported	Adverse reaction of drugs	Medication over dose, ph. defect
Who can report (staff)	Doctors, Pharmacists, Nurses	All government and private hospital staff
When it can be reported	Any adverse reaction if noticed	--
How to report	Through completely filled yellow form	--
Where it can be reported	Complete filled ADR form should be submitted to PVpI	--

3.4 Adverse Drug Reactions Monitoring Benefits

Monitoring and reporting programs of adverse drug reactions can outfit the following advantages:

a) It provides data about the safety & the quality of medications.
b) It provides plans for risk management.
c) It forestalls the anticipated adverse events and aids in estimating adverse drug reaction adherence.
d) It teaches medical services groups, i.e., pharmacists, nurses, & patients, regarding adverse events and initiates the realization of A.D.R.s.

The primary targets of monitoring adverse drug reactions are:

- Uncover the quality of medications.
- A.D.R.s frequency.
- Recognize hazard factors that lead to adverse events [23].

3.5 Hazard / Serious Adverse Reaction

A hazard / serious adverse event (S.A.E.s) in clinical trials is characterized as any untoward clinical event that occurred in any dose:

1) Leads to death.
2) Is perilous
3) Leads to patient hospitalization.
4) Prolong patient hospitalization existence.
5) Leads to congenital aberration/birth deformity [4].

Clinical trial investigators are committed to reporting these reactions in clinical review reports. Research recommends that these reactions are frequently insufficiently announced in freely accessible reports [24].

3.6 Drug Regulation and Pharmacovigilance

Medication safety affairs & pharmacovigilance are essential to everybody where clinical intervention affects his life. Strong medication regulatory configurations establish the national ethos of medication safety & for medication public trust. Besides approving new drugs, medication regulatory authorities have to address these issues:

- Clinical preliminaries
- All the traditional & complementary medicine, vaccines, etc. Must be safe.
- Creating communication lines among all gatherings related to the safety of medications & warrantying that these lines are always available & act efficiently, especially at crisis times [15].

Pharmacovigilance programs need strong controller connections to warranty authorities who are quite informed about safety affairs in ordinary practice that might be pertinent to future administrative activity. Regulators comprehend that pharmacovigilance assumes a particular and essential part in guaranteeing the ongoing safety of pharmaceutical items. Pharmacovigilance programs should be upheld enough to accomplish their goals.

To gain acceptance by the national drug regulatory authority, the new medication should pass through three obstacles. Adequate evidence is needed to demonstrate the new medication to be:

- It has high quality,
- Efficient.
- For the purpose that is proposed, it is safe.

While the initial two models should be met before any thought can be given to endorsement, the safety issue is less sure. Safety isn't outright, and it tends to be decided just corresponding to efficacy. There is plausible that uncommon yet genuine adverse effects (for example, those happening with a recurrence of, say, one of every 5,000) won't be identified in the pre-registration advancement of the medication. For instance, deadly blood dyscrasia in 1 out of 5,000 patients cured with a new medication is prone to be perceived later than 15,000 patients have been cured & monitored, given that the foundation frequency of such a response is zero or a causal relationship with the medication is straightforward [25].

3.7 Regulation of Clinical Trial

The number of clinical studies in developing countries has increased over the past years. In the United States of America, the number of clinical preliminaries almost multiplied somewhere between 1990 and 1998 [5]. Clinical studies in potential new medication treatments will probably increment much further with the

sequencing of the human genome. Likewise, there is a developing coalition between the scholarly world and pharmaceutical manufacturers. This has led to genuine and boundless worry over moral and scientific issues, for example [26-29].

- Possibility of benefit conflict.
- Deceptive patient recruitment practices.
- Insufficiency of informed assent
- Absence of ability to guarantee ongoing checking of clinical preliminaries and adherence to sound and moral clinical trial standards.
- Lack of reporting & adverse reactions management.

For policymakers (medication regulators), the changing patterns over late years in the lead of clinical preliminaries present extraordinary and urgent difficulties, especially in guaranteeing that the rights and patients' health and their societies are ensured. In their endorsement of clinical preliminaries, policymakers focus on the efficacy & safety of new medication being scrutinized. Likewise, they should focus on the prevailing norms of care and patient safety related to the proper institutional review boards (I.R.B.s). Prescriptions needed for illnesses like tuberculosis, HIV/AIDS, malaria, and meningococcus meningitis, and those that might have problematic or dubious adequacy - safety profile, require careful observation when previously brought for an enormous scope into societies [30].

3.8 Monitoring of Post-marketing Safety

It is commonly acknowledged that part of the method involved with assessing medication safety requires to occur in the post-marketing (endorsement) stage, assuming significant advancements are not to be lost in an unduly prohibitive administrative net. Judgment regarding whether and how this may happen lies with the regulators. The greater the national pharmacovigilance and adverse drug reaction reporting system, the more likely it is that prudent regulators will make decisions for the early release of new medications with the assurance of beneficial advances [31].

Regulation overseeing the regulatory cycle in many nations considers conditions to be put on endorsements, for example, a prerequisite that there ought to be nitty-gritty pharmacovigilance in the early years after a medication's release. Nonetheless, cautious safety observation isn't restricted to new medications or to critical remedial advances. It has a significant part to play in the presentation of generic medications and in rehashing the safety profile of older prescriptions already obtainable, where new safety issues might have emerged. While unconstrained reporting stays a foundation of pharmacovigilance in the regulatory climate and is fundamental for signal recognition, the requirement for more active surveillance has likewise become progressively clear.

Without data on use and the degree of utilization, unconstrained reports don't make it conceivable to decide the frequency of an A.D.R. owing to a drug or its safety according to a comparator. More precise and hearty epidemiological techniques that consider the constraints of unconstrained reporting are needed to address these important safety questions. They should be consolidated into post-marketing surveillance programs. Different parts of medication safety have been relatively ignored up to this point, which ought to be involved in observing latent and long-haul impacts of medications [32].

These include:

- Recognition of medication interactions
- Estimating the ecological load of drugs utilized in enormous populaces
- Evaluating the contribution of excipients (inactive ingredients) to the safety profile.
- Frameworks for comparing the safety profiles of comparative meds
- Observation of the adverse effects on humans of medication residues in animals,
- for example, hormones & antimicrobials.

Promotional activities:

Medication safety in the advancement stage is progressively impacted by the restrictions imposed by sponsors on the research policy, the lab program and the open sharing of data as the exploration schedule is negotiated with clinical associates [33]. There is developing public worries that nearby coordinated effort among academia and pharmaceutical manufacturers may antagonistically influence clinical practice and clinical studies [25,34,35].

A concerning advancement for medication safety is 'immediate to consumer' advertising by pharmaceutical producers, different medications

vendors, and parties with a personal stake. Spending on this action has multiplied in the U.S.A. in the course of recent years [27]. While it might develop patients' comprehension and be in line with the need to ameliorate access to medication data, the absence of reliability and precision might expose patient safety to risks. Indeed, even where direct advertising of prescriptions to patients is illicit, the Internet gives a medium that makes correspondence conceivable across borders. This may make general guidelines about advertising ineffectual. Internet sites presently make it possible to trade prescribed medications like benzodiazepines without controls. These improvements in internet correspondence affect the safety of the medication [36].

All of these affairs indicate the requirement for more careful observation of medication safety & examination of advertising. Assets and experience are essential to guarantee that promotional materials include exact and equiponderant data and moral practices. Self-guideline by industry is probably not going to be adequate in numerous nations. A territorial or global coordinated effort in executing a regulatory code of practice for pharmaceutical advertising items, supervised by an honest, consultative body, would help in such a manner [2].

Distortion and absence of complete revelation might have similarly significant and possibly genuine security suggestions. A joint article, which traces the reasoning for this approach, expresses that this activity is a reaction to the industry's undeniably close command over exploration, results, and, as a rule, regardless of whether and how results are made public [22].

Pharmacovigilance improvement:

1) Increment the consciousness of medical care experts and the general population on the comprehension of the significance of pharmacovigilance.
2) Create and advance a viable channel for A.D.R.s detailing, like an online reporting system.
3) Every one of the gatherings engaged with pharmacovigilance detailing is coordinated under a platform.
4) A unified data set for safety reports to simplify methodical development and definite investigations.
5) Further, develop correspondence among partners in the detailing of adverse reactions, for example, the controller, the medical care suppliers, and the producer for Pharmacovigilance [3].

4. CONCLUSION

Pharmacovigilance is the sole technique to ensure the safety of medicine throughout its life cycle. It is critical because clinical studies have limitations in detecting rare and very rare ADRs. The knowledge and information available regarding the safety of any drug is critical for drug regulators to make proper decisions to protect public health. The majority of ADRs are reported by healthcare providers. However, there is a significant rate of under-reporting documented internationally. It is today's most pressing issue. Despite these limitations, the spontaneous reporting system is the most extensively used approach for reporting ADRs and can produce signals for rare and extremely rare types of ADRs.

To make the world healthier than it is now if all healthcare providers regard ADR reporting as an ethical commitment and a substantial responsibility. Every report by a health care practitioner is crucial, even if the focus should be on the severe unlabeled forms of ADRs. There are considerable effects on PV to make it more functional after the concept has arisen, and we are moving closer to our destination by the day. It is our obligation to ensure that the pharmacovigilance system works appropriately. ADR reporting should be viewed as a critical duty, not an additional clinical burden, by healthcare practitioners to guarantee safer drug use around the world.

This manuscript is necessary for the scientific community. Pharmacovigilance is an essential part of current drug use, and there are common adverse drug reactions, so it is necessary to study the scope of pharmacovigilance and the establishment of drug guidelines to guide clinical use.

COMPETING INTERESTS

The authors declared that there is no conflict of interest regarding the publication of this paper and declare that they have no known competing financial interests or non-financial interests, or personal relationships that could have appeared to influence the work reported in this paper.

REFERENCES

1. Alsaedi AA, Younus MM. Gender Differences in Adverse Drug Reactions Among Adult Patients Reported to the Iraqi Pharmacovigilance Center. Iraqi Journal of Pharmaceutical Sciences (P-ISSN: 1683-3597, E-ISSN: 2521-3512). 2021;30(2): 249-260.
2. Mouton JP, Mehta U, Parrish AG, Wilson DP, Stewart A, Njuguna CW, Kramer N, Maartens G, Blockman M, Cohen K. Mortality from adverse drug reactions in adult medical inpatients at four hospitals in South Africa: a cross-sectional survey. Br J Clin Pharmacol. 2015;80(4):818-26. DOI: 10.1111/bcp.12567. Epub 2015 Jul 6. PMID: 25475751; PMCID: PMC4594724.
3. Food US. Drug Administration 2005. Guidance for industry: good pharmacovigilance practices and Pharmacoepidemiologic Assessment; 2019.
4. World Health Organization. The importance of Pharmacovigilance; 2002.
5. World Health Organization. International drug monitoring: the role of national centres, report of a WHO meeting [held in Geneva from 20 to 25 September 1971]. World Health Organization; 1972.
6. Helianildes Silva Ferreir. The importance of chemistry in pharmacovigilance 9th International Conference and Exhibition on Pharmacovigilance & Drug Safety. Munich, Germany; 2017.
7. Olsson S, Pal SN, Dodoo A. Pharmacovigilance in resource-limited countries. Expert Rev Clin Pharmacol. 2015;8:449–60.
8. Aronson JK, Hauben M, Bate A. Defining "surveillance" in drug safety. Drug Saf. 2012;35:347–57.
9. Guideline on good pharmacovigilance practives (G.V.P.). Product- or population-specific considerations. IV. Paediatric population. E.M.A./572054/2016 draft for public consultation. London: European Medicines Agency; 2017.
10. van Ramshorst MS, Kekana M, Struthers HE, McIntyre JA, Peters RP. Efavirenz-induced gynecomastia in a prepubertal girl with human immunodeficiency virus infection: a case report. B.M.C. Pediatr. 2013;13:120.
11. Njuguna C, Swart A, Blockman M, Maartens G, Chisholm B, Stewart A et al. Cases of antiretroviral-associated gynaecomastia reported to the National H.I.V. & Tuberculosis Health Care Worker Hotline in South Africa. AIDS Res Ther. 2016;13:40.
12. Surveillance of antiretroviral drug toxicity within antiretroviral treatment programmes. Geneva: World Health Organization; 2013. http://www.who.int/hiv/pub/arv_toxicity/ technical-brief-surveillance/en' Accessed 22 May 2018.
13. Oreagba IA, Usman SO, Olayemi SO, Oshikoya KA, Opanuga O, Adeyemo TA et al. Pharmacoepidemiology of antiretroviral drugs in a teaching hospital in Lagos, Nigeria. Ghana Med J. 2014;48:194–203.
14. Levi M, Sinisgalli E, Lorini C, Santomauro F, Chellini M, Bonanni P. The "Fluad Case" in Italy: Could it have been dealt differently?. Human Vaccines & Immune therapeutics. 2017;13(2):379-384.
15. Kumar MR, Bodhanapu S, Mani TT, Phaneendra P, Rahiman OF. Pharmacovigilance and its importance in drug regulation: An Overview. Der Pharmacia Lettre. 2011;3 (2):165-169.
16. Kim JH, Scialli AR. Thalidomide: the tragedy of birth defects and the effective treatment of disease. Toxicol Sci. 2011;122:1–6.
17. WHO operational package for assessing, monitoring and evaluating country pharmaceutical situations. Guide for coordinators and data collectors. Geneva: World Health Organization; 2007.
18. Hall M, Mc Cormack P, Aurthur N, Feely J. The spontaneous reporting of A.D.R.s by nurses. British journal of clinical pharmacology. 1995;40:173-175.
19. Patel A, Giles D, Thomas V, Gurubasavarajaswamy PM, Patel R. Pharmacovigilance: a review. International Journal of Pharmaceutical & Biological Archives. 2011;2(6):1569-74.
20. Sachdev Y. pharmacovigilance: safety matters, Indian pharmacology. February. 2008;40.
21. Moore N. The role of the clinical pharmacologist in the management of adverse drug reactions. Drug Safety. 2001;24(1):1-7.
22. Anusha L, Aashritha M, Teja K, Sridhar R. A review on pharmacovigilance and its importance. World J Pharm Pharm Sci. 2016;6(1):300-10.
23. Loannidis JP, Lau J. Completeness of safety reporting in randomized trials: an

evaluation of seven medical areas. JAMA. 2001;285(4):437-443.
24. Martin JB, Kasper DL, New England J. Med. 2000;343(22):1646-9.
25. Editorial, Safeguarding participants in clinical trials, Lancet, 2000, 355 (9222), 2177.
26. Angell M. New England J. Med., 2000, 342(20), 1516-8.
27. Angell M, New England J. Med. 2000;342(13):967-969.
28. Ioannidis JPA, Lau J, J. the American Medical Association. 2001;285(4):437-443.
29. White NJ. Proceedings of the XXVIIth CIOMS Conference, Geneva, Switzerland 14-15 Sep. 1993, Z. Bankowski, J.F. Dunne (eds) CIOMS, Geneva. 1994;126 – 135.
30. A fifth amendment for the Declaration of Helsinki, Lancet. 2000;356(9236):1123.
31. Meyboom RHB, Egberts ACG, Gribnau FWJ, Hekster YA. Drug Safety. 1999;21(6):429-447.
32. Good Pharmacovigilance Practice Guide, (MHRA); 2009.
33. Editorial, Lancet. 2000;356:781.
34. Al-Temimi AA, Krishnan S, Sandhu AK, Bangash NSA. Medication Nonadherence: Implications for patient health outcomes in pharmacy practice. Indonesian Journal of Pharmacy/ Majalah Farmasi Indonesia. 2021;32(4).
35. Dickman TF, Veit HR. Drug Benefit Trends. 2011;13 (1):48-52.
36. VOLUME 9A -of The Rules Governing Medicinal Products in the European Union-Guidelines on Pharmacovigilance for Medicinal Products for Human Use, (EMEA); 2008.

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