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A REVIEW ON PHARMACOVIGILANCE AND DRUG SAFETY MEASURES

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ABSTRACT

The World Health Organization (WHO) defines pharmacovigilance as the science and series of activities concerned with the detection, evaluation, and rejection of adverse effects or other drug-related problems, and a clinical test could be an analysis study in human volunteers to answer specific health questions. Clinical trials that are meticulously conducted are the quickest and safest way to implement treatment in individuals and improve health. Play a critical part in ensuring that the patient receives the safe medicine. Pharmacovigilance has been recognized as playing an important role in the judicious use of drugs by giving data on the harmful effects that drugs typically have on the population. The information on drug Adverse Drug Reactions (ADRs) is frequently increased by numerous suggests that such information studies, intensive observation, spontaneous reportage, and different new methods at the dictatorial and scientific levels square measure being developed with the intention of step-up Pharmacovigilance. Because assessment procedures contain some individual judgments, integrator reliability is frequently low. In conclusion, there is still no commonly acknowledged mechanism for assessing casualties from ADRs.

Keywords: Adverse drug reactions, Clinical test, Pharmacovigilance, Treatment.

1. INTRODUCTION

The World Health Organization defines pharmacovigilance as the science and activities related to the detection, assessment, understanding, and prevention of adverse effects or any other potential drug-related drawback, including both short- and long-term adverse effects of medications. Pharmakon, the Greek word for "drug," and vigilare, the Latin word for "to keep watch," are the words that give rise to the term "pharmacovigilance."

Pharmacovigilance has been practiced since 1998 and is not new to Asian countries.[1] When Asian countries made the decision to become members of the Uppsala Center for Adverse Event Monitoring. One crucial method for obtaining safety information for early detection is the spontaneous reporting of adverse medication reactions and adverse events. It is commonly acknowledged that before a medication is commercially released, it must first undergo several stages of testing to determine its safety and effectiveness. Clinical trials do have certain drawbacks, though. For example, their stringent inclusion and exclusion criteria require that they only be used on a very specific subset of patients; they do not examine specific population groups, such as children, pregnant women, or the mature population; and they may not have examined other factors that contribute to drug reactions, such as genetics, the environment, or drug-drug interactions.[2]

In addition to making patients more miserable, these adverse drug reactions (ADRs) significantly raise morbidity and mortality rates, placing a financial strain on society. It is estimated that 6.7% (0.1-0.85%) of hospitalized patients experience ADRs overall.[3] According to data, hospital stays are 8.25% longer and ADR-related death rates are 19.18% higher in patients with World Health Organization experiences. The average increase in total medical costs for patients with ADRs was 19.86%.[4]

The COVID-19 epidemic has had a greater influence on human life than any other event in the past century. It is a terrible major public health problem that is difficult and at times frightening. Unfortunately, there is no one medication treatment with established efficacy, and practically all pharmaceuticals being investigated are repurposed.[5]

The global community is frantic to find strategies to curb the spread of the new coronavirus and unearth a game changer. Interestingly, a web search for COVID 19 clinical trials found an ever-increasing number of clinical trials registered around the world. To address this unmet medical need, India's central regulatory authorities promptly launched a fast track assessment and approval mechanism for all clinical trial applications for COVID-19 medicines and vaccines. Furthermore, the changing norms of social isolation and lockdown during a pandemic may make traditional data collection methods ineffective. Recognizing the impact on various clinical trial-related activities, the central regulatory authorities allowed sponsors, investigators, and ethics committees to modify trial conduct while keeping participants' safety in mind, making mutual decisions on a case-by-case basis, and emphasizing the use of an electronic system. These notifications make the clinical trial procedure more adaptable and convenient in this extremely vulnerable condition. Although regulators recognize the difficulties, there is no relaxation in medication safety reporting. Pharmacovigilance efforts, particularly clinical safety reports, should continue as usual because patient safety remains the primary concern.[6]

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2. METHOD OF CAUSALITY ASSESSMENT

Many researchers have developed a variety of methods for assessing adverse drug reactions (ADRs) by misusing entirely different criteria, such as documented relationships between drug administration and ADR incidence, screening for non-drug related causes, in vivo or vitro test confirmation of the reaction, and previous data on similar events attributed to the suspected drug or to its therapeutic category, among other methods, to outline ADRs in several categories. However, there may be a lot of variation between and within raters because there aren't any defined diagnostic criteria or classes. There are currently no widely recognized methods for gaining access to ADR relationships. [7]

The three categories of activity that go under the umbrella of pharmacovigilance are academia, industry, and regulation. The goal of regulatory pharmacovigilance is to supply the public with medications that have a favorable benefit-harm profile. We will talk about some of the issues of regulatory post-marketing surveillance in this setting, then outline the techniques for finding new ADRs and weigh the benefits and drawbacks of each approach.[8]

- Dangaumou's French method 17
- Kramer et al. method 18
- Naranjo et al. methodology (Naranjo scale)19
- Balanced assessment method20
- Ciba-Geigy method21
- Loupi et al. method22
- Roussel Uclaf casuality assessment method23
- Australian method24

HISTORY OF PHARMACOVIGILANCE IN ASIAN NATION

In Asian countries, pharmacovigilance was instituted in 1986. A comprehensive Adverse Drug Reaction (ADR) monitoring system was established, encompassing twelve regional centers, each catering to a population of five million people. But no appreciable growth was produced. Subsequently, in 1997, Bharat became a member of the World Health Organization (WHO) and the Adverse Drug Reaction (ADR) program, which was examined and was mostly focused on two cities in the Kingdom of Sweden, but it was unsuccessful. For this reason, the National Pharmacovigilance Programme (NPPV) of Bharat was established in 2005 with funding from the World Bank and UN agency assistance. The successive advances in pharmacovigilance are displayed in table no. 1below.[9]

Table no.1 History of Pharmacovigilance

Year	Developments
1961	Worldwide tragedy due to thalidomide toxicity
1968	WHO research project for international Drug monitoring on pilot scale.
1996	Global standards level clinical trials initiated in India.
1997	India attached with WHO Adverse Drug Reaction Monitoring Program.
1998	Initiation of Pharmacovigilance in India.
2002	67th National Pharmacovigilance Center established in India.
2004-05	India launched National Pharmacovigilance Program.
2009-10	Pharmacovigilance Program (PVPI) started

DRUG SAFETY REPORTING

Given the enthusiasm, urgency, and hurry to develop effective medication treatments and vaccines for COVID 19, the question is, how do we ensure safety? Several new and old medications, ranging from anti-malaria to antiviral and immune-modulators, are being deployed and studied for clinical treatment and research, with the potential to affect newer coronaviruses. The use of medications on compassionate grounds, as well as exposing participants to investigational products with limited evidence of risk-benefit, highlights the importance of implementing thorough safety monitoring, adverse event reporting, and assessment measures. However, the bulk of trials conducted during the pandemic are primarily geared to establish clinical benefits and outcomes, with less emphasis on side events and safety concerns. On the other hand, no approved gold standard study design exists to identify a true drug safety risk. As a result, safety assessments are based on a variety of sources, including randomized controlled clinical trials, real-time observational studies, and spontaneous adverse event reports. This will assist policymakers decide whether to maintain or cease the use of the proposed drug(s) in clinical care and research. As a result, it is everyone's job to ensure and support the gathering of drug safety data in order to conduct timely reviews, causality assessments, and real-time signal

detection. Although this will provide a chance for pharmacovigilance professionals, doctors, and regulators to collaborate, evaluating suspected adverse event reports, particularly causality assessment, will be difficult.[10]

CAUSALITY ASSESSMENT OF DRUG SAFETY REPORTS

The primary goal of pharmacovigilance and suspected adverse event reporting is to discover the drug's risk profile as early as possible and identify the group at risk. The evaluation of safety reports includes determining the probability (causal association or link) of the relationship between exposure to medicine and the occurrence of adverse events. The first critical step is to suspect an adverse drug event (a causal relationship) and then "prove or disprove it." Traditionally, excitement for the assessment is based on the severity of the adverse event, the requirement for further steps to either patient(s), amend prescribing information (regulatory), and conduct additional confirmatory investigations. Formal algorithms and statistical methods are available for assessing causation; nevertheless, the WHO-UMC and Naranjo Probability Scale are commonly used and internationally approved for objective assessment. The assessment criteria are based on some specific features of the event of interest, such as the time between drug administration and the appearance of the event, the pharmacological characteristics of the suspected drug (pharmacokinetic and pharmacodynamic actions), medical plausibility (clinical presentation and supporting investigations), the likelihood or exclusion of other causes, de-challenge information, and re-challenge, if applicable. Aside from these, clinical judgment of experts is also required.[11]

CHALLENGES OF CAUSALITY ASSESSMENT

However, causality evaluation in pharmacovigilance is a difficult and time-consuming process. The complicated nature of adverse events, wide differences in clinical presentations, background frequency of the adverse event, characteristics of the illness process, and use of numerous medicines in the same temporal sequence, among other considerations, may make analysis difficult. It will be even more difficult with the current restrictions on physical contact, travel, and unrestricted movement, as well as isolation and quarantine during the epidemic. It may not be possible to record details of all events, reducing the completeness and quality of safety reports.[6] These reports may be missing critical data, such as a comprehensive description of the adverse event's start, features, and time course. Second, the suspicion is typically retroactive, and desirable baseline laboratory investigations are frequently unavailable. When the patient is treated outside, the de-challenge and result information are lost. It will be nearly impossible to apply algorithms to and assess these incomplete medication safety reports. The drug's adverse responses might range from mild symptoms to severe life-threatening or important medical events, and they can be infrequent or prevalent. The time between intervention and the appearance of an unfavorable event is an important factor. An adverse event occurring promptly following medication therapy demonstrates a strong causal relationship, whereas an AE occurring after a long latent period may be missed, necessitating long-term follow-up, proper resources, and experience for safety evaluation. Adverse events with a high background frequency, particularly fever, cough, and pneumonia at times of crisis, present a difficulty. Furthermore, drug-related adverse effects may be caused by a combination of causes. Concurrent use of medications with overlapping toxicities, previous medical conditions/co-morbidities, elderly individuals, and alcoholics may all be contributing or complicating variables. This necessitates a careful assessment of how much each of these factors contributes to the occurrence of adverse outcomes. Baseline laboratory testing and examinations, as well as regular monitoring, can undoubtedly help with assessment by ruling out probable other explanations. Given the massive clinical workload and lack of systematic monitoring throughout the pandemic, only a team of proactive specialists who rigorously adhere to treatment procedures will be able to record the specifics. The best illustration has been the outcry for the use of hydroxychloroquine in COVID-19 patients. Concomitant medicines (antimicrobials, antiviral, antifungal, diuretics, etc.) and electrolyte disturbances all have an effect on the QTc interval, including hydroxychloroquine. The drug's adverse responses might range from mild symptoms to severe life-threatening or important medical events, and they can be infrequent or prevalent. The time between intervention and the appearance of an unfavorable event is an important factor. An adverse event occurring promptly following medication therapy demonstrates a strong causal relationship, whereas an AE occurring after a long latent period may be missed, necessitating long-term follow-up, proper resources, and experience for safety evaluation. Adverse events with a high background frequency, particularly fever, cough, and pneumonia at times of crisis, present a difficulty. Furthermore, drug-related adverse effects may be caused by a combination of causes. Concurrent use of medications with overlapping toxicities, previous medical conditions/co-morbidities, elderly individuals, and alcoholics may all be contributing or complicating variables. Currently, the available data is insufficient to assess the safety and risk profile of combining medications in such a setting. Furthermore, the suggested COVID 19 medicines (antivirals) are metabolized via the cytochrome 3A4 route; either substrate or inhibitor could cause severe drug-drug interactions. To better comprehend these intricacies, the individual patient group should be tracked using predefined clear questions and objectives, as well as proper data collection technologies and an analytical plan.[9]

Unfortunately, causality assessment using algorithmic methods is confined to determining causality as "certain" or "unlikely" in the presence of several confounding variables. However, they are useful in determining the causal relationship between "possible" adverse medication reactions and their scientific basis. Often, "possible" is seen as a lower-level category. However, it means that there is evidence to support a "reasonable possibility" of a causal association between the medicine and the adverse event. When several of these thorough reports are combined, they can highlight risk factors that can be avoided or mitigated. After all, this is the most effective strategy to protect prospective end users.[10]

Three main aims of monitoring of suspected drug reactions were identified:

• Early warning of serious adverse reactions to drugs, especially those previously unsuspected

• Evaluation of drug hazard

• Research into mechanisms of drug action, to aid the development of safer and more effective drugs.[11]

The scope of the WHO drug monitoring programme was to

• "assess the feasibility or otherwise of an international system of drug monitoring;

• develop the methodology for recording case histories of adverse reactions to drugs, systems for analysis and feed-back of data to national monitoring centres;

• undertake analysis of in stored data on an experimental basis;

• provide facilities for searches by WHO staff and national centres on the 20 types and patterns of adverse reactions to individual drugs; and

• make a preliminary study of the contribution of drug monitoring to research in pharmacology and therapeutics"[12]

ADVERSE DRUG REACTION (ADRs)

An adverse drug reaction (ADR) is defined as an unintentional and hazardous health product that results at doses sometimes or is tested for the purpose of diagnosing, treating, or preventing a disease or changing an organic function. However, it might be challenging to identify the actuating agent associated with adverse drug reactions (ADRs) when they occur because they contain a lot of chemicals. When choosing whether or not to employ a specific medication in a patient, it is important to consider the risk factor in addition to the predicted benefits of the medical specialty [13]

Adverse drug reactions (ADRs) are classified in two ways

- Predictable (Type-A) Reaction
- Unpredictable (Type-B) Reaction

Predictable (Type-A) Reaction: - These square measurements validated the medicine's pharmacologic qualities, such as the drug's heightened yet statistically measurable reaction to its aspect effects, gynogenic effects, and withdrawal symptoms.

Unpredictable (Type-B) Reaction: - These included allergic reaction and specialty, and they were based on the patient's unique characteristics rather than the recognized effects of the medication. These are less frequent, usually unrelated to dosage, extremely dangerous, and need drug withdrawal. an inventory of some known and suspected medications with negative side effects. The recognized medication and its side effects are given in table no.2 below.

Table no.2 Drug and their ADR effect

Drug	Adverse Drug Reactions (ADRs)
Thalidomide	Phocomelia, Multiple defects
Methotraxate	Multiple defects, Foetal death
Androgen	Virilization, limb, esophageal, cardiac defects
Tetracyclines	Discoloured or deformed teeth, retarded bone growth
Warfarin	Nose, eye and hand defects, growth retardation
Aspirin/ Indomethacin	Premature closer of ductus arteriosus

The Role of Artificial Intelligence- From genetics to genomics, artificial intelligence (AI) will have a significant impact. AI will search through massive informational databases and medical records for trends, and it will help find mutations and connections to disease. Today, businesses are developing a new breed of computational technologies that can inform physicians about the consequences of genetic diversity, whether it be for therapeutic or natural purposes, on a cell's DNA. Consider the pharmacovigilance forecasting skills. All of this requires an understanding of 21st-century interoperability, which holds that various systems used by various groups of people can be used for a common goal

because those systems share standards and methodologies, in order for it to make sense, particularly in the context of pharmacovigilance.

We also need to acknowledge and welcome AI's capacity to decipher unusual data from social media and other sources of irregular notifications. AI will not only enable the pharmacovigilance community to transcend the use of Drug Utilization Studies as the only tool and drug recalls as the only course of action. When one considers the current state of biologics, both innovator and follow-on, the urgency of this scenario grows. The inefficiencies and lack of predictive capacity in the current developmental paths used to predict the risk profile of these medicinal goods, as well as the issues with indication extrapolation, interchangeability, and similarity, demonstrate the need for a stronger predictive tool set.[14]

CLINICAL TRIAL- A clinical trial may consist of an analysis study that evaluates an alternative medical treatment or a replacement method of treating an existing medical condition to see whether it will be more effective in stopping and screening for illness or treating it. 34.To get preliminary data on efficacy, toxicity, and pharmacokinetics, a broad range of doses of the research drug are administered to Associate in Nursing patients or to an in-vitro substrate 35.Figure No. 2 displayed the clinical trial study phase. Figure 2: Clinical trial phase Comprehensive pre-clinical research is carried out by pharmaceutical companies prior to initiating clinical trials for a medicine. 36. Studies Prior to Clinical Practice Pre-clinical research includes trials on an animal population as well as in vitro (i.e., tube or lab) investigations.[15]

Pre-clinical Trails- Pre-clinical research includes trials on an animal population as well as in vitro (i.e., tube or laboratory) investigations. To get preliminary efficaciousness, toxicity, and pharmacokinetic data and to assist pharmaceutical companies in determining whether or not to proceed with additional testing, a wide travel dose of the medication area unit study was provided.[16]

Clinical Studies

Phase-0- A first-in-human, exploratory trial carried out in compliance with the 2006 guidelines on experimental medicine published by the U.S. Food and Drug Administration (FDA) may have been designated as phase zero recently. Unique options for part zero trials include giving the study drug in single sub-therapeutic doses to a small group of subjects (10–15) in order to gather preliminary data on the agent's pharmacological medicine, or how the body processes the drug, and pharmacodynamics, or how the drug adds to the body.[17]

Phase-I- Unit for Phase I Path Area stage one of human subject testing. A small (20–80) healthy volunteer cluster is typically the most desirable. This section comprises trials aimed at evaluating the safety (pharmacovigilance), tolerability, pharmacological medicine, and pharmacodynamics of a medication.

There are Unit totally different styles of clinical trial trials.

- SAD: Single-ascending dose studies are ones in which a small group of participants get a single dosage of the medication while being observed and tested for a certain period of time.
- MAD: Studies on multiple ascending doses are carried out to improve understanding of the pharmacological medicine of numerous medication dosages.[18]

Phase-Il- Clinical trial trials are conducted on a large cluster of patients and volunteers (20–300) and are designed to evaluate the drug's efficacy as well as to continue clinical trial safety assessment in a larger cluster of patients and volunteers once the study drug's initial safety has been confirmed. Clinical trial A and B are the two main categories into which clinical trial studies are often separated. Clinical trial B is especially created to check efficaciousness, or how well the treatment works at the recommended dose (s), while clinical trial A is specifically styled to access dosing demands (what proportion drug ought to be given). Certain experiments combine clinical and non-clinical trials, examining the efficacy and toxicity of each. [19]

Phase III- Phase III studies are sporadic controlled multicenter trials with large patient clusters (300–3,000 or more, depending on the disease/medical condition studied), and they are designed to be the final determination of how effective a drug is when compared to the "gold standard" treatment currently in use.[21]

Phase IV- The Post-Promoting Police Work Trial is another name for the Phase IV trial. Phase IV trials include pharmaceutical vigilance, or security police work, and ongoing technical assistance for drugs that have been given the go-ahead to be sold. The purpose of the security police work is to monitor any infrequent or semi-permanent adverse effects over a much larger patient population and longer time period than was anticipated throughout the harmful effects identified by phase IV trials, which may result in a drug being banned from sale or limited to specific uses. A recent instance involves trogelitazone (Rezulin and Vioxx-vioxx) 35 and Baycol (branch names Bycol and lipobay).[22]

3. CONCLUSION

There is presently no widely recognized technique for determining the casualty of ADRs. Pharmacovigilance is the scientific study of a range of topics connected to the identification, assessment, comprehension, and prevention of

adverse effects or any other drug-related issue. Adverse drug reactions (ADRs) can be better understood through a variety of methods, including database studies, close observation, and impromptu reporting. Drug usage for compassionate purposes can eventually become the norm, endangering patient safety. More reliable, high-quality data are needed in order to produce high-quality evidence and conduct a prompt evaluation. All adverse occurrences and outcomes must be systematically monitored and reported in order to make meaningful causation and risk-benefit assessments that balance individual safety with scientific requirements. It is probable that during the pandemic, there will be a rise in the quantity of safety reports. An effective pharmacovigilance quick response expert team that evaluates medication safety reports every week and addresses problems right away can be helpful in dealing with this.

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