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AN OVERVIEW OF PHARMACOVIGILANCE INCIDENCES AND MANAGEMENT PRACTICES

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- **Keywords:** Introduction, History of Pharmacovigilance, Reporting of Adverse Drug Reactions, Development of Pharmacovigilance in India, Future challenges in Pharmacovigilance, Current scenario of Pharmacovigilance, Future challenges in pharmacovigilance, To study the awareness status about adverse drug reactions and its reporting through an online survey.

- **Abstract**

Over the past 175 years, there have been numerous advancements in the field of pharmacovigilance. The research and practices around the identification, evaluation, comprehension, and avoidance of side effects or any other drug-related issues are known as pharmacovigilance. This study was divided into two sections: Part A is a literature review, and Part B uses the online Surrey method. The development of pharmacovigilance and the steady increase in adverse reaction reporting are the main conclusions of the Part A study. Since the late 1950s and early 1960s thalidomide tragedy effects, pharmacovigilance has experienced significant modifications. and part B doesn't take reporting ADRs too seriously. As a result, more people need to be aware of ADR reporting.

1. Introduction

"The science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other possible drug-related problems" is how the World Health Organisation (WHO) defines pharmacovigilance. (1)

According to this broad definition, the goals of pharmacovigilance are to: prevent harm from adverse reactions in humans resulting from the use of authorised pharmaceuticals within or outside the terms of marketing authorization or from occupational exposure; and to promote the safe and effective use of pharmaceuticals, particularly by promptly informing patients, healthcare providers, and the general public about the safety of pharmaceuticals. Thus, pharmacovigilance is an activity that promotes patient safety and public health. (2)

Pharmacovigilance is necessary to track the effects of medications both during and after clinical trials and after they are released into the market, to keep an eye on the quality of medications, to recognise the health risks

associated with administering particular medications, to keep patients safe, and to determine the effectiveness of medications. (3) The research we carried out was split into two sections: Part B: Online Survey and Part A: Literature Survey.

The Aim and Objectives of the Study of Part A:

- To study the History of Pharmacovigilance
- To study the Reporting of Adverse Drug Reactions
- To study the Development of Pharmacovigilance in India
- To study the Current scenario of Pharmacovigilance
- To study the Future challenges in pharmacovigilance

The Aim and Objectives of the Study of Part B:

- To study the awareness status of adverse drug reactions and their reporting through an online survey.

2. History of Pharmacovigilance

2.1 Pharmacovigilance in 19th Century

Pharmacovigilance began 175 years ago on January 29, 1848, when Hannah Greener, a little girl from the north of England, passed away following the administration of a chloroform anaesthetic before the excision of an infected toenail. Chloroform was a more potent and safer anaesthetic, which Sir James Simpson developed and used in clinical practice. Although the reasons behind Hannah's death were looked into to comprehend what had happened to her, the cause of her death could not be determined. Most likely, pulmonary aspiration or a fatal arrhythmia claimed her life. A commission to address this issue was formed by The Lancet Journal in response to additional deaths and concerns expressed by physicians and the general public regarding the safety of anaesthesia. The panel urged all English physicians, including those practising in colonies, to report any fatalities brought on by anaesthesia. The findings were released in 1893 in The Lancet.

Pharmacovigilance monitoring advanced at a snail's pace throughout this time.

2.2 Pharmacovigilance in 20th Century

On June 30, 1906, the US Federal Food and Drug Act was created, establishing the need for medications to be clean and devoid of any impurities.

This organisation outlawed the use of fake medicinal indications for medications in 1911.

Diethyl glycol was the solvent of sulfanilamide elixir, which caused 107 deaths in the United States in 1937. The manufacturing businesses were unaware of the solvent's toxicity at the time, even though it was thought to be

the cause of death. As a result, in 1938 the Federal Food, Drug and Cosmetic Act was created to update the public health system. The new system anticipated the need to prove a drug's safety before approving it for sale and included the option to inspect factories.

Acetylsalicylic acid (ASA) was proposed by Douthwaite as a possible cause of melena in 1938. Different results were found in the investigation of ASA's gastrointestinal toxicity. ASA is currently not recommended for people who have gastrointestinal ulcers, nonetheless, it was demonstrated in 1955 that ASA can cause gastrointestinal disorders. Thalidomide Mishap

Following the tragedy of Thalidomide, European Pharmacovigilance underwent a significant shift in 1961. In a letter to the editor of the Lancet Journal, Australian physician Dr McBride proposed a link between thalidomide and congenital malformations in infants. Indeed, he noted that among pregnant women who had taken thalidomide, the incidence of congenital abnormalities in newborns (1.5%) had increased by as much as 20%. Simultaneously, at the Paediatric Convention in Germany, Dr. Lenz proposed a link between thalidomide and abnormalities, and his suspicion was reported in the German journal Welt am Sonntag.

Retrospective research conducted in 1973 demonstrated a link between thalidomide consumption during pregnancy and congenital abnormalities in newborns. The USA did not observe the thalidomide catastrophe since Dr. Kelsey expressed serious concerns regarding the drug's safety during pregnancy. The thalidomide catastrophe exposed several crucial concerns and problems, including the validity of animal testing, the actions of the pharmaceutical corporation, and the significance of continuing to monitor the drugs after they are marketed. Specifically, this event modifies the Pharmacovigilance system by making the spontaneous reporting of adverse drug reactions more structured, standardised, and methodical. All the necessary components were already there in this letter to create an informal report and demonstrate a causal relationship. The USA enacted an amendment in 1962 mandating that pharmaceuticals submit safety and efficacy data before premarketing submission. This change requires the inclusion of teratogenicity tests conducted on three separate animals in the safety data.

The "Yellow Card" (YC) was established in the United Kingdom in 1964. A particular form called YC is used to gather an informal report on drug toxicity.

Thalidomide's debacle in Europe in 1965 sparked the creation of EC Directive 65/65, a piece of legislation.

The Boston Collaborative Drug Surveillance Programme began with a pilot study in 1966. It was the first organisation to use in-hospital monitoring to perform epidemiologic studies to measure the possible side effects of medications, and it played a crucial part in the creation and use of techniques for drug epidemiology.

The WHO Programme for International Drug Monitoring was established in 1968, and the following 10 countries were involved: Australia, the United Kingdom, the United States, Germany, Canada, Ireland, Sweden, Denmark, New Zealand, and the Netherlands. In 1975, Italy took part in this programme. Between 1968 and 1982, a large number of investigations on documented adverse medication reactions were carried out.

The International Society of Pharmacovigilance (IsoP) was founded in 1992 after funding for the European Society of Pharmacovigilance (ESoP) was provided. This society's objectives were to advance pharmacovigilance and improve every facet of the responsible and safe use of medications.

The European Medicines Agency (EMA) was established in 1995.

2.3 Pharmacovigilance in 21st Century

EudraVigilance received funding in 2001. It is the official European database for tracking and evaluating reports of possible side effects of medications that are being investigated in European clinical trials or that have been approved for sale.

A significant shift in European Pharmacovigilance was noted in 2012 when Directive 2010/84/EU was implemented. The main changes in the new legislation were:

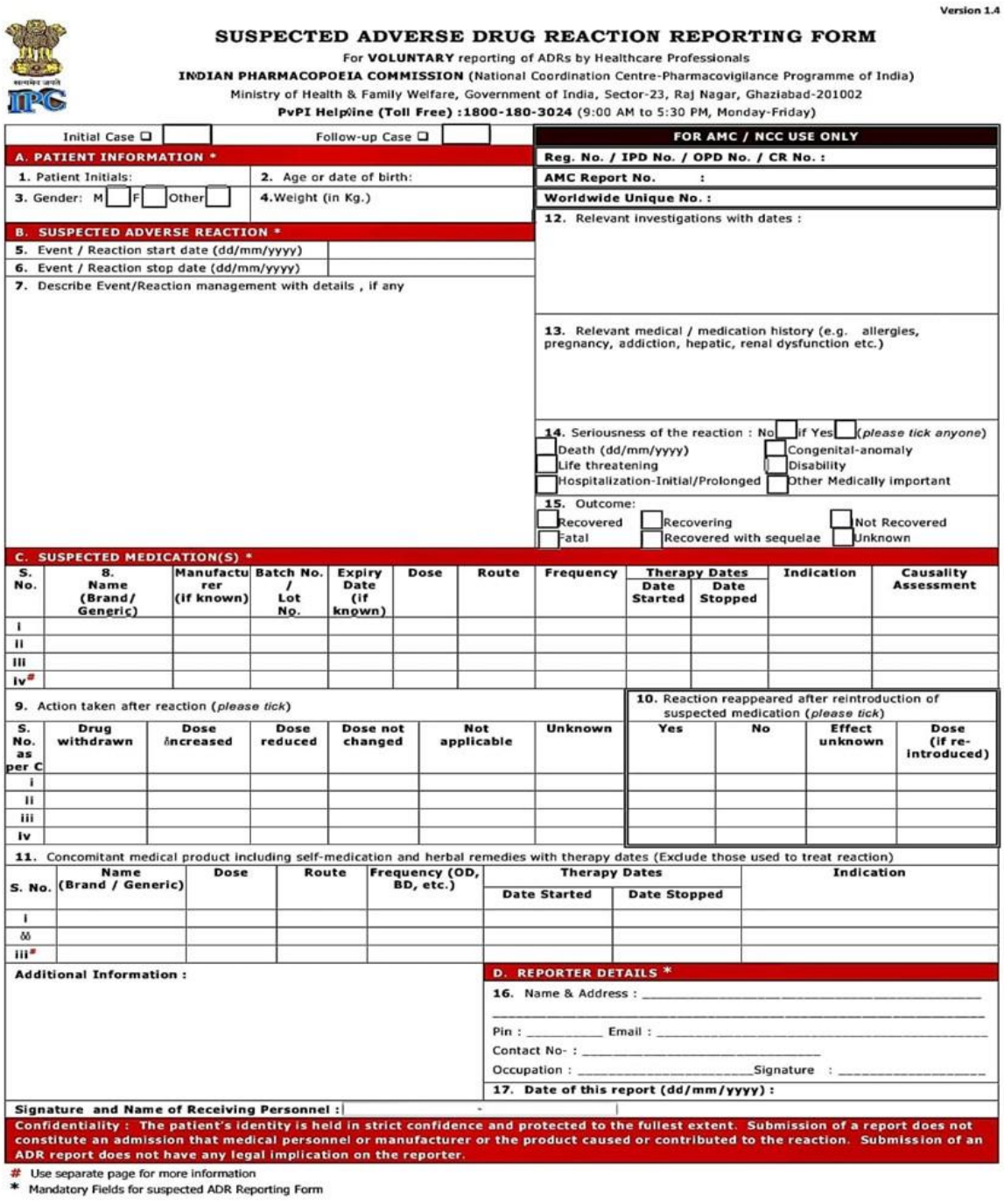
- Modification of the definition of adverse drug reactions (ADR);
- Greater involvement of patients and citizens in Pharmacovigilance activities; se-effect relationship between the adverse event and the drug
- Strengthening of the Eudravigilance database containing reports of suspected reactions reported by all EU Member States
- Increasing transparency and timeliness of important information on Pharmacovigilance problems
- Obligation of “additional monitoring” for the products contained in the specific list kept by the EMA
- Possibility to impose further safety and/or efficacy studies on the certificates of marketing authorization at the time of granting the trust

The new EudraVigilance format was introduced in November 2017, and marketing authorizations will have more access to the database to help them complete their pharmacovigilance requirements. According to Commission Implementing Regulation (EU) N. 520/20121, these responsibilities include the ongoing monitoring of EudraVigilance data and the reporting of validated signals to the Agency and national regulatory bodies.

3. Reporting of ADR

Fig: Reporting of Adverse Drug Reaction

3.1 Adverse Drug Reaction Reporting Form



Version 1.4

SUSPECTED ADVERSE DRUG REACTION REPORTING FORM

For **VOLUNTARY** reporting of ADRs by Healthcare Professionals

INDIAN PHARMACOPOEIA COMMISSION (National Coordination Centre-Pharmacovigilance Programme of India)

Ministry of Health & Family Welfare, Government of India, Sector-23, Raj Nagar, Ghaziabad-201002

PvPI Helpline (Toll Free) :1800-180-3024 (9:00 AM to 5:30 PM, Monday-Friday)

Initial Case ☐ Follow-up Case ☐

FOR AMC / NCC USE ONLY

Reg. No. / IPD No. / OPD No. / CR No. :

AMC Report No. :

Worldwide Unique No. :

A. PATIENT INFORMATION *

1. Patient Initials: 2. Age or date of birth:

3. Gender: M ☐ F ☐ Other ☐ 4.Weight (in Kg.)

B. SUSPECTED ADVERSE REACTION *

5. Event / Reaction start date (dd/mm/yyyy)

6. Event / Reaction stop date (dd/mm/yyyy)

7. Describe Event/Reaction management with details , if any

12. Relevant investigations with dates :

13. Relevant medical / medication history (e.g. allergies, pregnancy, addiction, hepatic, renal dysfunction etc.)

14. Seriousness of the reaction : No ☐ If Yes ☐ (*please tick anyone*)

☐ Death (dd/mm/yyyy) ☐ Congenital-anomaly

☐ Life threatening ☐ Disability

☐ Hospitalization-Initial/Prolonged ☐ Other Medically important

15. Outcome:

☐ Recovered ☐ Recovering ☐ Not Recovered

☐ Fatal ☐ Recovered with sequelae ☐ Unknown

C. SUSPECTED MEDICATION(S) *

S. No.	8. Name (Brand/ Generic)	Manufacturer (if known)	Batch No. / Lot No.	Expiry Date (if known)	Dose	Route	Frequency	Therapy Dates		Indication	Causality Assessment
								Date Started	Date Stopped		
i											
ii											
iii											
iv#											

9. Action taken after reaction (*please tick*)

S. No. as per C	Drug withdrawn	Dose increased	Dose reduced	Dose not changed	Not applicable	Unknown
i						
ii						
iii						
iv						

10. Reaction reappeared after reintroduction of suspected medication (*please tick*)

Yes	No	Effect unknown	Dose (if re-introduced)

11. Concomitant medical product including self-medication and herbal remedies with therapy dates (Exclude those used to treat reaction)

S. No.	Name (Brand / Generic)	Dose	Route	Frequency (OD, BD, etc.)	Therapy Dates		Indication
					Date Started	Date Stopped	
i							
ii							
iii#							

Additional Information :

D. REPORTER DETAILS *

16. Name & Address : _____

_____

Pin : _____ Email : _____

Contact No- : _____

Occupation : _____ Signature : _____

17. Date of this report (dd/mm/yyyy) :

Signature and Name of Receiving Personnel :

Confidentiality : The patient's identity is held in strict confidence and protected to the fullest extent. Submission of a report does not constitute an admission that medical personnel or manufacturer or the product caused or contributed to the reaction. Submission of an ADR report does not have any legal implication on the reporter.

Use separate page for more information

* Mandatory Fields for suspected ADR Reporting Form

Fig. Suspected Adverse Drug Reaction reporting form

4. Development of Pharmacovigilance in India

i. Under the direction of the Indian Drug Controller, pharmacovigilance was first implemented in India in 1986 with the official launch of the Adverse Drug Reaction Monitoring System. The program's primary goal was to collect data on adverse responses using various reporting methods, particularly unplanned reporting. Nonetheless, at that time, there were 12 major centres, each housing over 50 million people. Delhi, Mumbai, Lucknow, Chandigarh, Pondicherry, and Kolkata were among the locations of several of the centres. These primary health centres were to be associated with district hospitals and primary health posts.

ii. The WHO Programme for International Drug Monitoring, which is run by the Uppsala Monitoring Centre in Sweden, underwent a substantial revision in 1997 when India joined.

iii. Nevertheless, the government's regulatory bodies brought the Pharmacovigilance programme back to life for the second time in the nation's history. There were six centres nationwide, including New Delhi (which was named the National Centre and is housed at the All-India Institute of Medical Sciences), Mumbai (a special centre at the King Edward VII Memorial Hospital), Lucknow, Kolkata, Chandigarh, Aligarh, and Delhi, Mumbai, Lucknow, Chandigarh, Luckicherry, and Kolkata. These primary health centres were to be associated with district hospitals and primary health posts.

iv. The World Bank-funded National Pharmacovigilance Programme of India (PvPI), which is sponsored by WHO, was launched in India on January 1st, 2005. The World Bank provided funding of 0.1 million USD annually for a duration of five years, and on November 23, 2004, the Pharmacovigilance programme in India was formally established and put into effect.

v. The Central Drug Standard Control Organisation (CDSCO), India's national regulatory body, houses the National Pharmacovigilance Advisory Committee, which assists in coordinating the reporting of adverse drug reactions. The adverse reaction reports from the nation were to be directed via two primary centres: the North East Zonal Centre (Department of Pharmacology, All India Institute of Medical Sciences, New Delhi) and the South West Zonal Centre (Department of Clinical Pharmacology, King Edward VII Memorial Hospital, Mumbai). Three regional centres would report to the South West Zonal Centre in addition to collecting reports on its own.(6)

5. Current Scenario of Pharmacovigilance

India is an immense country and there are drug brands more than 6,000 licensed drug manufacturers and over 60,000 branded formulations. A high-level discussion with a combination of stakeholders,

a) i.e., Ministry of Health and Family Welfare
b) Indian Council of Medical Research
c) Medical Council of India
d) Pharmacy Council
e) Nursing Council
f) Dental Council

g) Pharmaceutical Companies
h) Consumer Associations
i) Nongovernmental Organizations

Patient groups need to be started to inform them of the plans being made by the Drug Control General of India (DCGI) to enhance and develop a comprehensive system for pharmacovigilance and to bolster the DCGI office with qualified medical and scientific assessors. Officials working in the DCGI's Pharmacovigilance department as well as in the peripheral, regional, and zonal centres should receive extensive training covering all facets of the field. Training should be planned twice a year as part of this ongoing activity. establishing a single, universally applicable adverse event reporting form for the entire nation.

New opportunities for national and international collaborations that can improve post-marketing surveillance programmes and enhance drug safety have emerged in conjunction with Pharmacovigilance organisations to enhance drug safety through the advancement of information technology (IT). An illustration of a global partnership to create a standardised post-marketing surveillance database is the Uppsala Monitoring Centre (UMC). The approach is predicated on the sharing of adverse reaction data across 80 national drug monitoring centres.

5. Future challenges in pharmacovigilance

Even though most industrialised nations have strong pharmacovigilance systems and the essential institutions and procedures of a framework in place, they nevertheless struggle to keep track of adverse drug reactions (ADRs) brought on by biosimilars or generic medications.

Most of the ADR are caused due to following categories of drugs:

I) Cardiovascular Drugs

Worldwide, cardiovascular disease (CVD) and hypertension are the two main causes of death and morbidity. With an estimated 1.27 billion people, India has roughly 30 million coronary artery disease (CAD) patients, of which 14 million live in urban areas and 16 million in rural ones. By 2020, India's CVD burden will surpass that of other global regions. More than 30% of deaths occur each year as a result of CVD. CVD-related mortality is expected to increase to 4.2 million deaths by 2030. The rate at which CVD-related death and morbidity are rising is concerning. The longer the patients stay on polypharmacy, the higher the risk of adverse drug reactions (ADRs). Research has indicated that 18–24% of patients with CVD had ADRs.

II) Antidiabetic Drugs

Diabetes is another illness that is affecting a lot of people worldwide, much like CVD. Diabetes currently affects 415 million people globally, and by 2040, that figure is expected to surpass 642 million. Over 65.1 million people in India have received a diagnosis of the illness, and projections indicate that by 2030, there will be 89 million sufferers, with roughly 56% of them coming from metropolitan areas.

III) Antipsychotic Drugs

In India, the usage of antipsychotic medications has increased due to a rise in the incidence and prevalence of psychiatric diseases. Antipsychotic medications impact various dopaminergic pathways, which has led to the observation of adverse drug reactions (ADRs) in hospital-based, retrospective, prospective, and community-based studies conducted in India and overseas. These include neurological, gastrointestinal, and reproductive disorders that worsen patients' quality of life. When prescribing antipsychotic medications, the study's researchers advise using caution. However, information about the precise prevalence and scope of the issue in India is insufficient.

IV) Combination Products

Adverse event reporting related to the use of combination medications, such fixed-dose combos (FDCs), has proven to be difficult in India. The presence of five or more medications in FDC formulations makes it extremely challenging to determine the time link between a drug and an occurrence. In the current situation, however, the clinical experience and knowledge of the healthcare personnel is used to determine the causality of adverse events linked to FDCs.

Adverse event reporting using diagnostics is another new difficulty. As medical device adverse event reporting via the MvPI is still in its infancy, facts necessary for root-cause investigation might not become available for several years. (8)

Age-related physiological changes in the geriatric population may have an impact on the drug's pharmacokinetics and pharmacodynamics, which may alter the drug-response connection. Due to their frequent comorbidities and concurrent therapy, elderly people are more vulnerable to side effects.

To comprehend the changes in pharmacokinetic and pharmacodynamic characteristics associated with medication action in the body, drug safety research in paediatrics is necessary. (6)

EXPERIMENTAL WORK

Methodology

- **Study design-** A descriptive cross-sectional survey was designed.
- **Study setting-** The research study was carried out among the undergraduate students of two colleges Dr RG Bhoyar Institute of Pharmaceutical Education and Research, Wardha and Smt. Radhikabai Meghe Memorial College of Nursing, Sawangi Meghe, Wardha. We have not classified them in male and female.
- **Materials and methods-** It was an online survey conducted using google forms.
- **Study population-** 250 participants
- **Study duration-** 19 April 2023 To 22 June 2023
- **Google form link-**

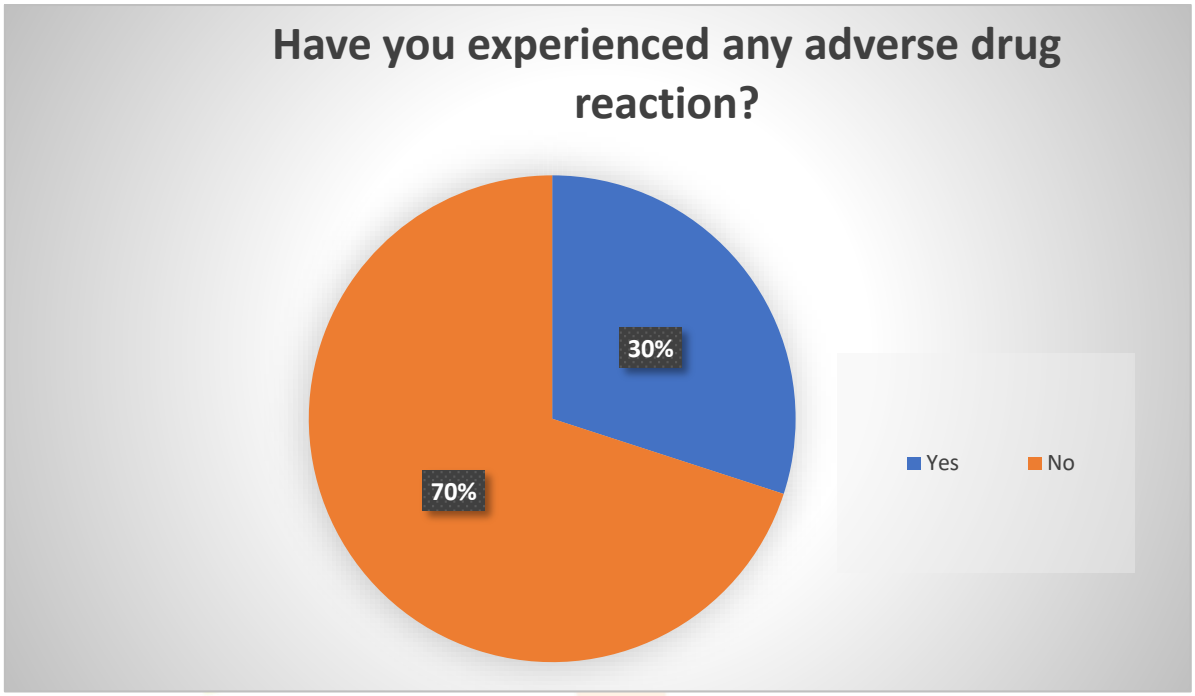
https://docs.google.com/forms/d/1tDT_qZyG4MiVpMW_JR_HQR9aLZp2nyxykvU-TdhQpCQ/edit?chromeless=1#responses

Questionnaires

1) Have you experienced any adverse drug reactions?

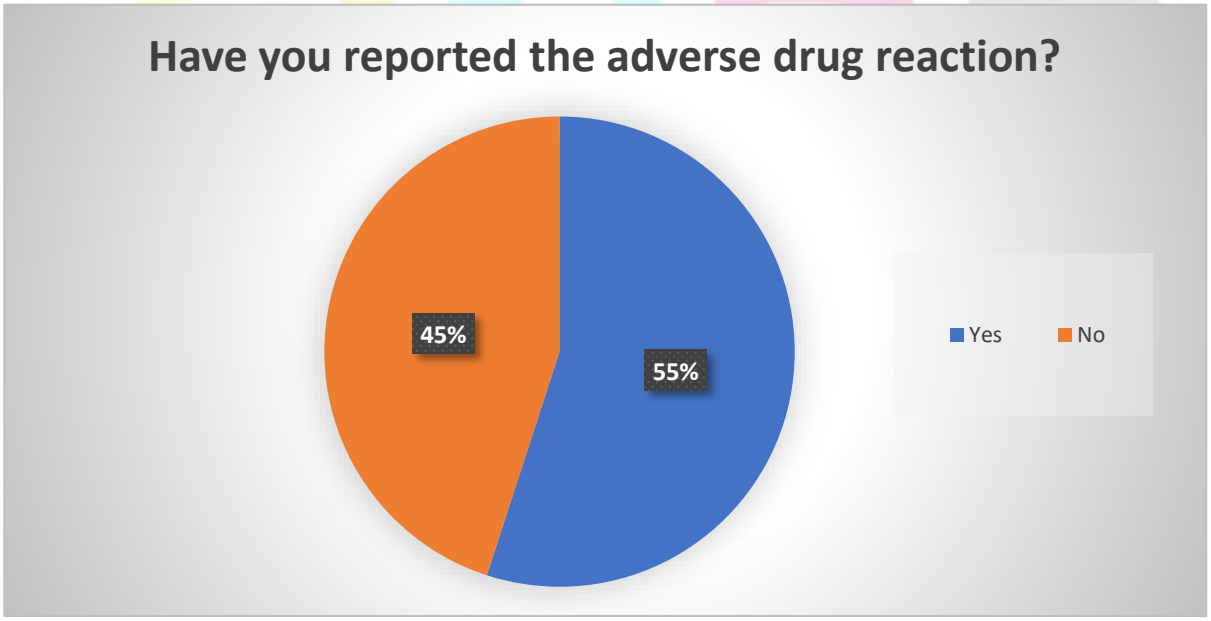
2) Have you reported the adverse drug reaction?

OBSERVATIONS:



The chart above shows that of the 250 participants, 30% had an adverse drug reaction.

In the chart above, it was found that among all participants, 55% reported adverse drug reactions, while 45% did not.



SUMMARY

"An Overview of Pharmacovigilance Incidences and Management Practices" is the title of our project. This investigation was carried out in two phases. The literature review in Part A and the online survey method in Part B. Our Part A study's main conclusions are that pharmacovigilance has been established and that there has been a steady increase in the number of adverse drug reaction reports. In Part B, undergraduate students from two colleges participated in an online survey to gauge their knowledge of ADRs and the need for reporting them.

RESULT AND DISCUSSION FOR PART A

The current systematic analysis verified that while pharmacovigilance monitoring (PvPI) advanced slowly in the past, it later developed and PvPI was founded. PvPI is now a major player in collecting data linked to drug safety and sending it to the WHO database for updates.

RESULT AND DISCUSSION FOR PART B

The purpose of this study was to measure participant knowledge of ADRs and ADR reporting. ADRs were reported by 16% of participants, out of the 30% who had encountered them, according to a significant study finding. Of the participants, 14% are aware of adverse drug reactions and have reported them to their doctor, while the remaining participants have chosen to ignore them.

CONCLUSION FOR PART A

This research demonstrates the significant transformations that the field of photovoltaics has experienced since the fallout from the thalidomide disaster in the late 1950s and early 1960s. And India was where pharmacovigilance development got its start.

CONCLUSION FOR PART B

It demonstrates that participants do not take reporting ADR seriously. As a result, more people need to be aware of ADR reporting. When compared to the level of illiteracy, even literate persons appear to be less likely to recognise ADRs. This demonstrates the lack of concern for people's health.

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