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A REVIEW ARTICLE ON PHARMACOVIGILENCE

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ABSTRACT

Pharmacovigilance is like a sunshade to describe the processes for monitoring and evaluating ADRs and it is a key component of effective drug regulation systems, clinical practice and public health programs. The number of Adverse Drug Reactions (ADRs) reported resulted in an increase in the volume of data handled, and to understand the pharmacovigilance, a high level of expertise is required to rapidly detect drug risks as well as to defend the product against an inappropriate removal. The current global network of pharmacovigilance centers, coordinated by the Uppsala Monitoring Centre, would be strengthened by an independent system of review.

This would consider litigious and important drug safety issues that have the potential to affect public health adversely beyond national boundaries. Recently, pharmacovigilance has been confined, mainly to detect adverse drug events that were previously either unknown or porly understood. Pharmacovigilance is an important and integral part of clinical research and these days it is growing in many countries. Today many pharmacovigilance centers are working for drug safety monitoring in this global pitch, however, at the turn of the millennium pharmacovigilance faces major challenges in aspect of better safety and monitoring of drugs.

In this review we will discuss about drug safety, worldwide pharmacovigilance centers and their role, benefits and challenges of pharmacovigilance and its future consideration in healthcare sectors. All drugs have the capacity to cause adverse effects and no drug is completely safe.Pharmacovigilance (PV) plays a key role in the healthcare system through assessment, monitoring and discovery of interactions amongst drugs and their effects in human. Pharmaceutical and biotechnological medicines are designed to cure, prevent or treat diseases; Thus, for safety medication ADRs monitoring required for each medicine throughout its life cycle, during development of drug such as pre-marketing including early stages of drug design, clinical trials, and post-marketing surveillance.

1. INTRODUCTION

Pharmacovigilance is defined as the science of detection, assessment, understanding, and prevention of adverse effects of drugs or other related problems. The importance of pharmacovigilance was first highlighted in 1848, when a girl named Hannah Greener from England passed away after being administered chloroform for anesthesia to remove an infected toenail. Due to concerns around the safety of using anesthetics, the Lancet set up a commission to tackle this issue, encouraging doctors to report deaths caused by anesthesia.`

In 1961, McBride from Australia wrote to the Lancet, reporting his suspicion of thalidomide ingestion during pregnancy causing an increase in congenital malformations in babies[1]. Thalidomide was marketed in 1957 to alleviate morning sickness and was deemed to be safe for use during pregnancy by the manufacture. However, thalidomide use during pregnancy resulted in abnormal fetal development and limb deformities (phocomelia) in 46 countries worldwide. This highlighted the importance of safety monitoring of drugs post-marketing, independent of any industrial influence. The thalidomide tragedy served as a catalyst for the formation of the World Health Organization (WHO) International Drug Monitoring Program and the strengthening of regulatory frameworks on drug safety. From this incident, the spontaneous reporting of adverse drug reactions (ADRs) became systematic, organized, and regulated.

The WHO-Uppsala Monitoring Centre (WHO-UMC), based in Sweden, was established in 1978. It manages Vigibase, a WHO global database of individual case safety reports. It has over 18 million reports of suspected adverse effects of medicines submitted since 1968 by member countries of the WHO Program for International Drug Monitoring. This database can be used to evaluate the association between various medications and related ADRs. Medication safety monitoring was especially important during the coronavirus disease 2019 (COVID-19) pandemic to determine the safety of drugs, including new drugs, such as remdesivir, or repurposed drugs, such as lopinavir/ritonavir, against COVID-19.

Pharmacovigilance is used to detect, assess, understand, and prevent the adverse effects of medications. The need for safety monitoring has evolved around unfortunate incidents in history, with deaths caused by anesthesia and congenital malformations from thalidomide use. Reports from adverse drug reactions (ADRs) are stored in a global database and can be used to evaluate the associations between various medications and associated ADRs. Clinicians

play an important role in the recognition and reporting of ADRs to national pharmacovigilance centers (NPCs). The purpose of NPCs is to make the clinicians understand their functions, including the monitoring, investigation, and assessment of ADR reports, along with periodical benefit-risk assessments of medications via multiple sources. A case study on NPCs and the types of safety issues evaluated by them are provided to illustrate their role in medicine safety surveillance. ADR monitoring was also combined with vaccine safety surveillance approaches. Overall, this study will provide insights to clinicians on the importance of pharmacovigilance in maintaining patient safety with the proper use of medications.

2. PHARMACOVIGILANCE IN DRUG RELATION

Pharmacovigilance programs made strong by links with regulators. Regulators understand that pharmacovigilance plays a specialized and pivotal role in ensuring ongoing safety of medicinal products.

Clinical trial regulation:

In recent years there has been a substantial increase in the number of clinical trials in developed and developing countries. In their approval of clinical trials, regulatory bodies look at safety and efficacy of new products under investigation. Safety monitoring of medicines in common use should be an integral part of clinical practice. Education and training of health professionals in medicine safety, exchange of information between national pharmacovigilance centers, the coordination of such exchange, and the linking of clinical experience of medicine safety with research and health policy, all serve to enhance effective patient care. A regular flow and exchange of information in this way means that national pharmacovigilance programmes are ideally placed to identify gaps in our understanding of medicine-induced diseases. [11]

Post marketing safety drug monitoring:

These includes detection of drug interactions, measuring the environmental burden of medicines used in large populations, assessing the contribution of 'inactive' ingredients to the safety profile, systems for comparing safety profiles of similar medicines, surveillance of the adverse effects on human health of drug residues in animals, e.g. antibiotics and hormones. The Council for International Organizations of Medical Sciences (CIOMS) report on benefit-risk assessment of medicines after marketing has contributed to a more systematic approach to determining the merit of available medicines.[12]

Pharmacovigilance in national drug Policy:

The provision of good quality, safe and effective medicines and their appropriate use is the responsibility of national governments. Multidisciplinary collaboration is of great importance in particular, links need to be forged between various departments of the ministry of health and also with other stakeholders, such as the pharmaceutical industry, universities, nongovernmental organizations (NGOs) and those professional associations having responsibility for education on rational use of medicines and pharmacotherapy monitoring.

Pharmacovigilance in Disease Control Public Health Programmes:

The monitoring of medicine safety in countries where there is no regulatory or safety monitoring system in place, or in remote areas with little or no health care surveillance or infrastructure, has been identified as a matter for concern. The problems are especially apparent in situations that involve the use of medicines in specific communities, for example, for the treatment of tropical diseases such as malaria, leishmaniasis and schistosomiasis, and for the treatment of HIV/AIDS and tuberculosis. Pharmacovigilance should be a priority for every country with a public health disease control programs.[13]

PHARMACOVIGILANCE AND INTERNATIONAL HEALTH

The current global network of pharmacovigilance centers is coordinated by the Uppsala Monitoring Centre, would be strengthened by an independent system of review. This would consider contentious and important drug safety issues that have the potential to affect public health adversely beyond national boundaries. The Erice Declaration provides a framework of values and practice for collection, analysis and subsequent communication of drug safety issues. Today, the burden of ADRs on public health despite the progress in pharmacovigilance that has been made, the burden on public health of ADRs remains significant. Pharmacoeconomic studies on the costs of adverse reactions suggest that governments pay considerable amounts from health budgets towards covering costs associated with them. However, it has become increasingly clear that the safety profile of medicines is directly linked with socio-political, economic and cultural factors that in turn affect access to medicines, their utilization patterns and public perceptions of them.[14,15]

Drug utilization: Drug utilization patterns are a major determinant in drug safety. For instance, the use of injectable medicines is more common in developing countries. Direct advertizing to the consumer of prescription medicines has become commonplace in many countries. With this information patients feel more able to make their own therapeutic

decisions, without assistance from doctor or pharmacist. The result has been increasing self medication, licit and illicit sale of medicines over the Internet, and over- prescribing by doctors on patients' demand. This has had considerable effect on increased prescribing. Such public health programmes, however, need not focus only on patients but could be used for the benefit of the general public as well. Such awareness-building and educational initiatives should also include children and elderly populations and could be greatly facilitated through partnerships with the media, educational institutions, governmental and non-governmental organizations. The success of WHO International Drug Monitoring Programmes is entirely dependent on the contributions of national pharmacovigilance centers. Ideally every country should have a pharmacovigilance centre.[16]

PRE-MARKETING CLINICAL TRAILS

Safety monitoring in clinical trials involves collecting adverse events, laboratory investigations and details of the clinical examination of patients. Pharmacovigilance staff may be involved to varying degrees in all phases of clinical trials, including the planning, execution, data analysisand reporting of safety information. Safety issues from animal pharmacology and toxicology studies, findings in phase I studies, known ADRs with similar drugs, signals from other studies and special patient groups, (e.g. the elderly) need to be addressed. The practice of collecting all adverse events rather than suspected ADRs arose from the failure of clinical trials to detect serious reactions with practolol and after several years experience this is now the approach adopted by companies in most studies. The involvement of pharmacovigilance staff in clinical trials also includes an important responsibility for the expedited reporting of individual cases and safety updates required by the UK Medicines Control Agency (MCA) and other regulatory authorities.[17,18]

Well conducted clinical trials should be able to identify and characterise common type A (pharmacologically mediated) ADRs, indicate how these are tolerated by patients, determine a relationship between ADRs and dose or plasma concentration and identify pre-disposing (risk) factors if at all possible. These issues will usually be presented and discussed in an integrated safety analysis and clinical expert report in the Marketing Authorisation Application submitted by the company and will be the basis of ADRs, warnings and precautions included in the prescribing information i.e. Summary of Product Characteristics (SPC) or data sheet.[19]

3. ROLE OF PHARMACOVIGILANCE DATA

Pharmacovigilance data plays a pivotal role in assessing the safety of drugs throughout their lifecycle. This data encompasses information on Adverse Drug Reactions (ADRs), medication errors, and other safety-related issues. Here's how pharmacovigilance data contributes to identifying and mitigating drug risks[24,25]

Early detection of adverse events: Pharmacovigilance databases collect data from healthcare providers, patients, and regulatory authorities. Analyzing this data allows researchers to detect adverse events that may not have been identified during clinical trials. Early detection enables timely intervention to prevent further harm to patients.[26]

Signal detection: Pharmacovigilance experts use statistical and analytical tools to detect signals or patterns that suggest a potential safety concern. These signals prompt further investigation into the safety of a specific drug, leading to risk mitigation strategies.

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Risk assessment: Once a potential risk is identified, pharmacovigilance data helps assess the severity and frequency of the adverse events. This assessment guides regulatory authorities and healthcare providers in making informed decisions about drug use.[27]

Labeling updates: Pharmacovigilance data often results in updates to drug labels, including warnings, precautions, and contraindications. These label changes provide healthcare professionals and patients with important safety information.[28]

Risk minimization strategies: In some cases, pharmacovigilance data may lead to the development of risk minimization strategies, such as restricted distribution programs or Risk Evaluation and Mitigation Strategies (REMS), aimed at ensuring the safe use of certain medications. Withdrawal or market restrictions: In extreme cases, pharmacovigilance data may prompt regulatory agencies to withdraw a drug from the market or impose restrictions on its use to protect patient safety.

Case studies in pharmacovigilance

Several high-profile cases highlight the significance of pharmacovigilance data in mitigating drug risks:

Thalidomide: The thalidomide tragedy in the 1960s, where the drug caused severe birth defects, emphasized the importance of rigorous post-marketing surveillance. This incident led to the establishment of comprehensive pharmacovigilance systems.[29]

Vioxx: The withdrawal of the painkiller Vioxx in 2004 due to an increased risk of cardiovascular events illustrates how pharmacovigilance data can influence regulatory decisions to protect public health.

Rofecoxib (Cox-2 Inhibitors): Pharmacovigilance data prompted regulatory agencies to closely scrutinize Cox-2 inhibitors, leading to label changes and warnings about their cardiovascular risks.[30]

Future directions in pharmacovigilance

As the technology and data collection methods continue to advance, pharamacovigilance is evolving. Here some directions:

Big data analytics:

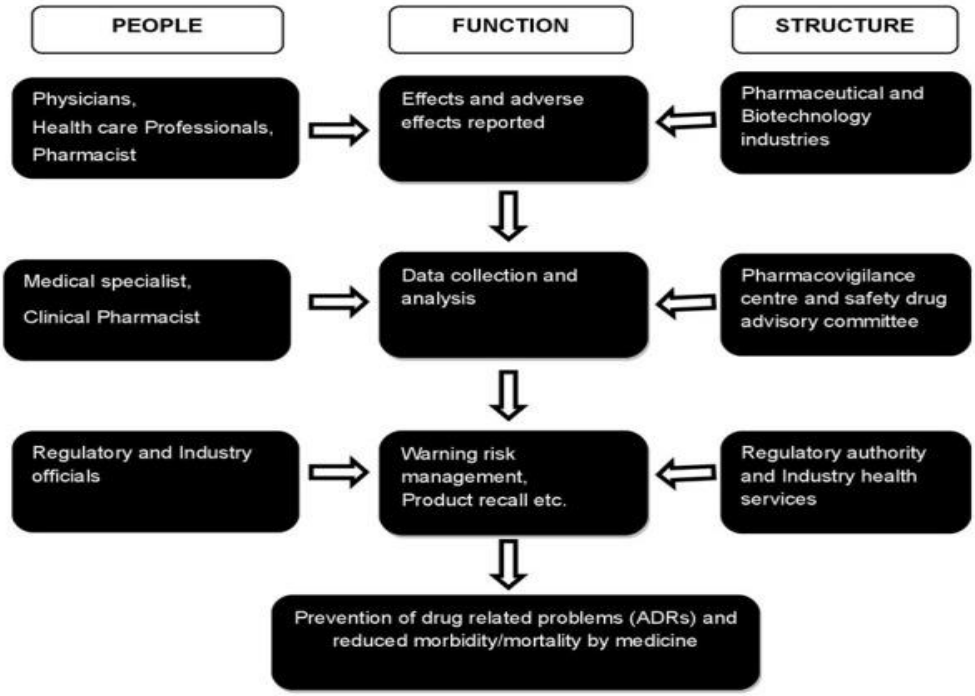
Leveraging big data analytics and machine learning will enhance the ability to detect subtle safety signals and trends in pharmacovigilance data.[31]

Real-world evidence:

The integration of real-world evidence, such as electronic health records and patient-reported outcomes, will provide a more comprehensive view of drug safety in diverse patient populations.

Global collaboration:

Pharmacovigilance efforts are increasingly becoming global collaborations, allowing for the sharing of data and expertise to identify and mitigate drug risks worldwide.



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ADR DATA FLOW:

ADR reports were collected at the AMC by the PV staff who checked for validity of the report and conducted provisional causality assessment. The ADR forms are then dispatched to the coordinating center. The AMC staff maintains a log of all the activities of the center and the selected AMCs also carry out focused ADR monitoring of drugs as per the watch list. The coordinating centers are conducting causality assessment and upload the reports into the PV database. The coordinating center also prepare a consolidated report of ADRs collected at defined time intervals and then implement and integrate PV activities into public health programs involving mass usage of drugs. Finally, the integrated ADR data is then transmitted through VigiFlow interface into the UMC adverse reaction database where signal processing can be carried out (Lindquist 2008). Programme communication of ADR data flow is shown below. There is a quality review panel which ensures the quality of ADR data that has been constituted for maintaining quality assurance in the program. All the centers will be assessed based on performance metrics criteria, completeness of reports, training imparted, and other parameters mentioned in the PV program protocol.[36]

4. FUTURE PROSPECTS

As future prospects increase, PV systems capable to detect new ADRs, and taking regulatory actions are needed to protect public health. Little emphasis has been put into generating information that can assist a healthcare professional or a patient in the decision-making process. The gathering and communication of this information is an important goal of PV. Information about the safety of drug active surveillance is necessary. When develop new methods for active post- marketing surveillance, one has to keep in mind that the important to collect complete and accurate data on every serious reported event. Spontaneous reporting is a useful tool in generating signals, but the relatively low number of reports received for a specific association makes it less useful in identifying patient characteristics and risk factors. PV methods must also be able to describe which patients are at risk of developing an ADR. As a source of information, the PV approach would be consistent with the growing patient involvement in drug safety. The PG could play a role in identifying individual risk factors for the occurrence of certain ADRs. In the future, PV has to concentrate on the patients as a source of information in addition to the more traditional groups, such as the health professionals. At present, the DCGI should act quickly to improve PV so as to integrate Good Pharmacovigilance Practice (GPP) into the processes and procedures to help ensure regulatory compliance and enhance clinical trial safety and post marketing surveillance. An appropriately working PV system is essential if medicines are to be used carefully. It will benefit healthcare professionals, regulatory authorities, pharmaceutical companies and the consumers. It helps pharmaceutical companies to monitor their medicines for risk. Post-marketing PV is currently a challenging and laborious process, not only industry-wide, but also for regulatory agencies. The aim of the PV is to receive the information, documentation of the work and knowledge online while giving priority to the new and important safety issues. Non-serious events have less priority than serious events but important in comparing the changes in health, although they are also screened routinely. In present time, GlaxoSmithKline has created a powerful new approach to PV, integrating traditional, case-based PV methods with disproportionality and data visualization tools. These tools exist within a system framework that facilitates in-stream review, tracking of safety issues and knowledge management. This very innovative tool and the processes will help to advance PV by improving efficiency and providing new analytical capabilities. Similar approach may be adopted by pharmaceutical companies for prompt detection and analysis of ADRs. Transparency and communication would strengthen consumer reporting, which are positive steps towards involving consumers more in PV.

5. CONCLUSION

The PV in India has become an important public health issue as regulators, drug manufacturers, consumers, and healthcare professionals are faced with a number of challenges. The PV in India continues to grow, evolve, and improve. India is the largest producer of pharmaceuticals and now emerging as an important clinical trial hub in the world. Apparently, the requirements for professional specialization, a combined view on PGx and clinical requirements are needed.

That helps to identify factors that increase the risk of unwanted outcomes from drug therapy and prior to commencing drug treatment and in tailoring drug treatment for individual patients. The PV has also involved in Data Mining Technology in spontaneous reports submit to the national surveillance systems.

The PVPI is coordinated at IPC through NCC under the control of Indian Government to generate an independent data on safety of medicines, which will be at par with global drug safety monitoring standards. National and regional PV systems are well-adapted bodies, attuned to the intricate collection and analysis of ADR data that leads to timely alerts and interventions to protect population health. Furthermore, it is responsible in India of entire campaign to improve PV knowledge and increase the number of ADRs reports up to the gold standard level established by the WHO. The

adverse events reported by PV system will potentially benefit to the community due to their proximity to both the population and public health practitioners, in terms of language and knowledge of the lifestyle and habits of patients, enables easy contact with reporters, for example by telephone, Email, text massages by mobile phones. The development of new and effective medicinal products makes a positive contribution to the health and well being of individuals. However, there is a need to improve PV systems to more effectively monitor and take action on safety issues associated with medicines to enhance their contribution to public health. Hence, PV for medicinal product safety to help the patients get well and to manage optimally or ideally, avoid illness is a collective responsibility of industry, drug regulators and clinicians and other healthcare professionals. The financial support and future projects should help to achieve a more comprehensive PV activity in India.

6. REFERENCES

[1] McBride WG. 1961. Thalidomide and congenital abnormalities. Lancet. 278, 1358 10.1016/S0140-6736(61)90927-8 [CrossRef] [Google Scholar]

[2] Coulter DM. The New Zealand intensive medicines monitoring programme in proactive safety surveillance. Pharmacoepidemiol Drug Saf. 2000;9:273– 80. [PubMed] [Google Scholar]

[3] Lared NL. Pharmacists' role in reporting adverse drug reactions in an international perspective. 2003. Available from: http://www.lareb.nl/documents/pds2004_1291.pdf [last cited on 2010 Jan 28] [PubMed]

[4] Olsson S. The role of the WHO Programme for International Drug Monitoring in coordinating worldwide drug safety efforts. Drug Saf. 1998;19:1– 10. [PubMed] [Google Scholar]

[5] Coulter DM. The New Zealand intensive medicines monitoring programme in proactive safety surveillance. Pharmacoepidemiol Drug Saf. 2000;9:273– 80. [PubMed] [Google Scholar]

[6] Mackay FJ. Post-marketing studies: The work of the drug safety research unit. Drug Saf. 1998;19:343–53. [PubMed] [Google Scholar]

[7] Folb PI, ten Ham M. Drug monitoring in developing countries: A drug regulator's perspective. Drug Inf J. 1995;29:303–5. [Google Scholar] Regulator's perspective. Drug Inf J. 1995;29:303–5. [Google Scholar08. Moore N. The role of the clinical pharmacologist in the management of ADRs. Drug Saf. 2001;24:1–7. [PubMed] [Google Scholar]

[8] Hall M, McCormack P, Arthurs N, Feely J. The spontaneous reporting of ADRs by nurses. Br J Clin Pharmacol. 1995;40:173–5. [PMC free article] [PubMed] [Google Scholar

[9] Hall M, McCormack P, Arthurs N, Feely J. The spontaneous reporting of ADRs by nurses. Br J Clin Pharmacol. 1995;40:173–5. [PMC free article] [PubMed] [Google Scholar]10. Hornbuckle K, Wu HH, Fung MC. Evaluation of spontaneous adverse event reports by primary reporter: A 15-year review (1983 to 1997) Drug Inf J. 1999;33:1117–24. [Google Scholar]

[10] WHO Policy Perspectives on Medicines. Geneva: WHO; 2004. Geneva: World Health Organization. Looking at the Pharmacovigilance: ensuring the safe use of medicines. Available from: http://www.whqlibdoc.who.int/hq/2004/WHO_EDM_2004.8.pdf [cited on 2009 Dec 15] [Google Scholar]

[11] Cioms CH. Geneva. Benefit-risk balance for marketed drugs. Evaluating safety signals: Report of CIOMS working group IV CIOMS, Geneva. 1998. Available from: http://www.cioms.ch/publications/g4-benefit-risk.pdf [last cited on 2010 Jan 15]

[12] WHO Policy Perspectives on Medicines. Geneva: WHO; 2004. Geneva: World Health Organization. Looking at the Pharmacovigilance: ensuring the safe use of medicines. Available from: http://www.whqlibdoc.who.int/hq/2004/WHO_EDM_2004.8.pdf [cited on 2009 Dec 15] [Google Scholar]

[13] Avorn J, Solomon DH. Cultural and economic factors that (mis)shape antibiotic use: The nonpharmacologic basis of therapeutics. Ann Intern Med. 2000;133:128–35. [PubMed] [Google Scholar]

[14] Ball LK, Evans G, Bostrom A. Risky business: Challenges in vaccine risk communication. Pediatrics. 1998;101:453–8. [PubMed] [Google Scholar]

[15] WHO Policy Perspectives on Medicines. Geneva: WHO; 2004. Geneva: World Health Organization. Looking at the Pharmacovigilance: ensuring the safe use of medicines. Available from: http://www.whqlibdoc.who.int/hq/2004/WHO_EDM_2004.8.pdf [cited on 2009 Dec 15] [Google Scholar

[16] Wallander MA. The way towards adverse event monitoring in clinical trials. Drug Safety. 1993;8:251–262. [PubMed] [Google Scholar]

[17] Medicines Act 1968. Guidance notes on applications for clinical trial exemptions and clinical trial certificates. MCA. 1996. pp. 94–99

[18] Rawlins MD, Thompson JW. Mechanisms of adverse drug reactions. In: Davis DM, editor. Textbook of adverse drug reactions. 4. Oxford University Press; 1991. pp. 18–45. [Google Scholar]

[19] Rawlins MD, Jefferys DB. Study of United Kingdom product licence applications containing new active substances, 1987–9. Br Med J. 1991;302:223–225. [PMC free article] [PubMed] [Google Scholar]

[20] Talbot JCC. Drug safety—a shared responsibility. Edinburgh: Churchill Livingstone; 1991. Spontaneous reporting; pp. 37–45. [Google Scholar]

[21] Henry D, Lim LY, Rodriguez LAG, et al. Variability in risk of gastrointestinal complications with individual non-steroidal anti-inflammatory drugs: results of a collaborative meta-analysis. Br Med J. 1996;312:1563–1566. [PMC free article] [PubMed] [Google Scholar]

[22] Edwards R, Wiholm BE, Martinez C. Concepts in risk-benefit assessment. A simple merit analysis of a medicine? Drug Safety. 1996;15:1– 7. [PubMed] [Google Scholar]

[23] Roma P, Monaro M, Colasanti M, Ricci E, Biondi S, Di Domenico A, et al. A 2-month follow-up study of psychological distress among Italian people during the COVID-19 lockdown. Int J Environ Res Public Health. 2020;17(21):8180. [Crossref] [Google Scholar] [PubMed]

[24] Wang N, Li Y, Wang Q, Lei C, Liu Y, Zhu S. Psychological impact of COVID-19 pandemic on healthcare workers in China Xi'an central hospital. Brain Behav. 2021;11(3):2028. [Crossref] [Google Scholar] [PubMed]

[25] Huang L, Wang Y, Liu J, Ye P, Chen X, Xu H, et al. Factors influencing anxiety of health care workers in the radiology department with high exposure risk to COVID-19. Med Sci Monit. 2020;26:926008-926011. [Crossref] [Google Scholar] [PubMed]

[26] Alonso J, Vilagut G, Mortier P, Ferrer M, Alayo I, Aragón-Peña A, et al. Mental health impact of the first wave of COVID-19 pandemic on Spanish healthcare workers: A large cross-sectional survey. Rev Psiquiatr Salud Ment. 2021;14(2):90-105. [Crossref] [Google Scholar] [PubMed]

[27] Mazza C, Colasanti M, Ricci E, Di Giandomenico S, Marchetti D, Fontanesi L, et al. The COVID-19 outbreak and psychological distress in healthcare workers: The role of personality traits, attachment styles, and sociodemographic factors. . Sustainability 2021;13(9):4992.[Crossref] [Google Scholar]

[28] Długosz P. Factors influencing mental health among American youth in the time of the Covid-19 pandemic. Pers Individ Dif. 2021;175:110711. [Crossref] [Google Scholar] [PubMed]

[29] Gómez-Salgado J, Andrés-Villas M, Domínguez-Salas S, Díaz-Milanés D, Ruiz-Frutos C. Related health factors of psychological distress during the COVID-19 pandemic in Spain. Int J Environ Res Public Health. 2020;17(11):3947. [Crossref] [Google Scholar] [PubMed]

[30] Sahebi A, Nejati-Zarnaqi B, Moayedi S, Yousefi K, Torres M, Golitaleb M. The prevalence of anxiety and depression among healthcare workers during the COVID-19 pandemic: An umbrella review of meta-analyses. Prog Neuropsychopharmacol Biol Psychiatry. 2021;107:110247.

[31] Hauben M. 2004. Application of an empiric Bayesian data mining algorithm to reports of pancreatitis associated with atypical antipsychotics. Pharmacotherapy. 24, 1122-29. 10.1592/phco.24.13.1122.38098 [Abstract] [CrossRef] [Google Scholar]

[32] Harpaz R, DuMouchel W, Shah NH, Madigan D, Ryan P, et al. 2012. Novel Data-Mining Methodologies for Adverse Drug Event Discovery and Analysis. Clin Pharmacol Ther. 91, 1010-21. 10.1038/clpt.2012.50 [Europe PMC free article] [Abstract] [CrossRef] [Google Scholar]

[33] Moride Y, Haramburu F, Requejo A, Begaud B. 1997. Under-reporting of adverse drug reactions in general practice. Br J Clin Pharmacol. 43(2), 177 81. [Europe PMC free article] [Abstract] [Google Scholar]

[34] Biswas P, Biswas AK. 2007. Setting Standards for Proactive Pharmacovigilance in India: The Way Forward. Indian J Pharmacol. 39, 124-28. 10.4103/0253-7613.33431 [CrossRef] [Google Scholar]

[35] Lindquist M. 2008. VigiBase, the WHO Global ICSR Database System: Basic Facts. Drug Inf J. 42, 409-19. [Google Scholar]