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Review Article

Pharmacovigilance Research in India: A Five-Year Literature Review

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Pharmacovigilance in India is developing rapidly since the last decade. Academic healthcare professionals have been conducting research in Pharmacovigilance as a routine academic activity. There is a need for advanced Pharmacovigilance research to understand and effectively manage the burden of drug induced illnesses in the Indian population. This review is aimed at highlighting Pharmacovigilance research published by Indian Pharmacologists since last five years. The literature published by Pharmacologists was searched in PubMed and extracted information from 35 articles were categorized and described based on affected organ system by adverse drug reactions (ADRs), drug classes involved, population studied, medication errors, and Pharmacovigilance system aspects. Majority of the studies published included patients from hospital settings predominantly from tertiary care centres. Nearly all studies were carried out in a single centre and were self-funded. There is scope for applying established pharmacovigilance methods, multicentre studies, research in community settings & public health programmes; expand the research activities to monitor drug induced adverse birth outcomes, adverse events following immunisation, safety monitoring of blood & blood products and medical devices to achieve the ultimate goal of ensuring Patient Safety.

Keywords: Pharmacovigilance; Safety Monitoring; Indian Pharmacologists

Introduction

Drug discovery and development process requires careful safety monitoring at every phase of any clinical trial. Post-authorization where medicines are used in real-world it is all the more important to monitor the safety of medicines. Hence, Pharmacovigilance is an important aspect of drug discovery and development process. World Health Organisation (WHO) defines Pharmacovigilance as "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug related problems" (World Health Organization). The scope of pharmacovigilance was widened to include blood products, biological products, medical devices, vaccines, herbal, traditional and complementary medicines (Essential Medicines and Health Products Information Portal).

Thalidomide tragedy in 1961 drew major attention to the safety issues with use of medicines. Pharmacovigilance aims at improving patient safety, by generating drug safety data from the adverse drug reactions (ADRs) and other drug related problems. In the post-marketing scenario it largely relies on spontaneous reporting by health care professionals and patients to health authority and marketing authorisation holders. Communication and management of risks identified through drug safety data analysis enhances pharmacotherapeutic knowledge, modifies prescribing patterns and improves patient safety.

WHO's Programme for International Drug Monitoring was started in 1968 with Uppsala Monitoring Centre, Sweden as a collaborating centre for improving the patient safety globally by communicating the safety signals identified through analysis of global ADR data. Currently, 156 countries participate in the programme, contributing to more than 16 million ADR reports in VigiBase (Uppsala Monitoring Centre). Pharmacovigilance Program of

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India (PvPI) was established in July, 2010 with an intention to improve patient safety and welfare in Indian population by monitoring drug safety and thereby reducing the risk associated with the use of medicines. Recently, PvPI was identified as a 'WHO Collaborating Centre for Pharmacovigilance in Public Health Programmes and Regulatory Services' (Indian Pharmacopoeia Commission).

Pharmacovigilance methods like passive surveillance, active surveillance, stimulated reporting, comparative observational studies, targeted clinical investigation and descriptive studies are applied for research in Pharmacovigilance. The data which is generated from research in Pharmacovigilance will provide the new knowledge or better understanding of the existing drug information to improve the benefit-risk profile of medicines.

In India pharmacovigilance is currently in evolving stage and but is developing rapidly since the last decade. It has taken a long-time for the country to establish the PvPI. However, since last three decades, the academicians have been conducting research in pharmacovigilance as part of academic activities. The expertise developed through such research has been useful for successful implementation and operations of PvPI. However, there is an earnest need for advanced Pharmacovigilance research to understand and effectively manage the burden of drug induced illnesses among Indian population. This literature review is aimed at highlighting the Pharmacovigilance research conducted and published by Indian Pharmacologists since last five years.

Research in the Area of Pharmacovigilance

A comprehensive literature search was performed in PubMed from 1st January 2012 to 31st July 2017 to identify the articles published in the area of Pharmacovigilance from India. The search strategy included medical subject headings (MeSH) "Pharmacovigilance" OR "Drug-Related Side Effects and Adverse Reactions" OR "Adverse Drug Reaction Reporting Systems" OR "Medication Errors" AND "India". We included research articles published in the area of Pharmacovigilance by researchers from Department of Pharmacology of any Indian medical institution either as corresponding author or co-author.

The literature search resulted in 144 titles and abstracts, of which 45 were excluded as they were not relevant to the current review on Pharmacovigilance. Of the 99 potentially relevant full-text articles retrieved, 64 were excluded as they were not published by researchers from Department of Pharmacology as corresponding author or co-author. Based on the objective of research work, extracted information from resulted 35 articles was categorized into (i) Cutaneous adverse drug reactions; (ii) Adverse drug reactions in specific population; (iii) Drug classes and adverse drug reactions; (iv) Medication errors; (v) Pharmacovigilance system; and (vi) Other studies related to adverse drug reactions.

Cutaneous Adverse Drug Reactions

The review found four research studies on cutaneous ADRs. A cross-sectional observational study in oral and maxillo-facial surgery and general medicine department with outdoor patients found that antibiotics and NSAIDs contributed to 40 (53%) and 30 (40%) of the total 75 skin reactions, respectively. Maculo-papular rash, urticaria, fixed drug eruption and angioedema were the most common reactions observed in this study with anticonvulsants induced Steven-Johnson syndrome (SJS) predominantly in general medicine department patients (Chattopadhyay and Chakrabarti, 2012). A study in dermatology department outdoor patients in Eastern India observed morbilliform eruption [16 (30.2%)], fixed drug eruption [13 (24.5%)], and Stevens-Johnson syndrome (SJS) and/or Toxic Epidermal Necrolysis (TEN) [13 (24.5%)] as most common cutaneous ADRs observed among 53 patients. Sulphonamides were reported to cause majority [9 (17%)] of cutaneous ADRs, followed by fixed-dose combinations of fluoroquinolones with nitroimidazoles [6 (11.3%)], analgesics [6 (11.3%)], antiepileptics [6 (11.3%)], beta-lactam antibiotics [5 (9.4%)], fluoroquinolones [4 (7.5%)], allopurinol [4 (7.5%)], and macrolides [3 (5.7%)] (Saha *et al.*, 2012).

Polypharmacy and multiple comorbid conditions were identified as important predisposing factors for causing cutaneous ADRs in a retrospective study conducted to analyse suspected cutaneous ADRs to systemic drugs. Maculopapular rash (46.3%) was the most commonly observed reaction and antibiotics [69 (51.5%)] were majorly implicated drug class out of

134 cutaneous ADRs identified in this study (Chopra *et al.*, 2015). Most of the cutaneous ADRs were exanthematous eruptions type [37 (33.3%)] and were reported with antimicrobial agents [77 (69.4%)] out of 111 cases of cutaneous ADRs reportedin another retrospective study. This study included both indoor and outdoor patients with suspected cutaneous ADRs (Dimri *et al*., 2016).

Stevens-Johnson Syndrome (SJS) accounted for 59 (3.3%) of 1769 ADRs in a retrospective study conducted at B.J. Medical College, Ahmedabad. In this study, patients receiving treatment for epilepsy (25), HIV (14) and upper respiratory tract infection (6) were common ADR victims. Among 59 SJS cases, four patients died and the suspected drugs in these patients were phenytoin, roxithromycin, amoxicillin, cloxacillin, cefotaxime and nevirapine (Patel *et al*., 2012). Clinical features of SJS and drug classes associated SJS were analysed in a prospective hospital-based study in Ahmedabad. Anti-bacterials for systemic use, anti-inflammatory, antirheumatics and antiepileptics were commonly associated (8 of 29 cases, each) with SJS. Ibuprofen and carbamazepine were involved in 5 (17.2%) and 4 (13.8%) cases. In two patients, SJS progressed to TEN and of which one led to death and the other developed conjunctival xerosis. A total of six patients in this case series developed long-term complications, conjunctival synechia (4), conjunctival xerosis (1), and urethral stricture (1) (Bang *et al*., 2012). A systematic review carried out by taking the published evidence of drug-induced SJS and TEN in Indian population from electronic databases identified ocular [27 (40.3%)] and septicemia [12 (17.7%)] as common SJS complications out of a total of 68 SJS/TEN. This study also found antimicrobials [145 (37.3%)], anti-epileptics [139 (35.7%)] and non-steroidal anti-inflammatory drugs (NSAIDS) 62 (15.9%) as most implicated drug classes; carbamazepine [71 (18.3%)], phenytoin [52 (13.4%)], fluoroquinolones [33 (8.5%)] and paracetamol [24 (6.2%)] as most commonly implicated drugs in SJS/TEN (Patel *et al*., 2013).

Adverse Drug Reactions in Specific Population

The review encompassed studies in patients from the departments like coronary care, psychiatry, paediatrics, and rheumatology. A retrospective cohort study to determine the frequency, risk factors, clinical spectrum and drugs associated with ADRs in the coronary care unit patients identified 152 (25.5%) ADRs in 595 patients with potentially preventable ADR rate of 45%. Renal dysfunction, arrhythmias, and polypharmacy were identified as ADR predictors. Hypokalemia/ hyperkalemia [43 (22%)], bleeding [22 (11%)] and cardiac arrhythmias [22 (11%)] were the commonest ADRs, and ADR rate was highest with streptokinase [19 out of 32 prescriptions (59.4%)]. This study revealed 2.8 days of additional hospital stay in patients with ADRs (Devi *et al*., 2012). Another retrospective study identified no significant gender-based differences in ADR patterns ($p>0.05$) in coronary care unit patients. But, this study found that the patients aged ≥60 years had a higher rate of ADRs ($p=0.013$) than patients aged 18-59 years (Kunnoor *et al*., 2014).

The most commonly reported ADR, incriminated pharmacology group and drug were extra-pyramidal movement disorders [22 (22.68%)], atypical antipsychotics [41 (35.62%)] and escitalopram [16 (13.91%)], respectively among 97 ADRs spontaneously reported in the psychiatry department of a tertiary care teaching hospital. In this study, the overall and serious ADR occurrence rate was 0.69% and 0.18%, respectively. Typical anti-psychotics were identified as an important risk factors for serious ADRs (Patel *et al*., 2015). Out of total 673 Adverse Drug Events (ADE), antipsychotics (72%) were the most frequently involved medication classes to cause ADE, majority (87%) of ADE were central nervous system disorders, and sedation (41%) was the most commonly reported ADE in a cross-sectional survey in 400 ambulatory patients with mental disorders. This study also reported high rate [343/400 (86%)] of ADE occurrence and significant ($p<0.05$) body weight gain in patients receiving atypical antipsychotic drugs (Kumar *et al*., 2017).

A prospective intensive surveillance study in the pediatric ward of a public teaching hospital aimed to assess off-label use as a risk factor for ADRs found higher percentage (67%) of ADRs due to off-label use compared to labelled use (33%) (OR 2.84, 95% CI 1.37-7.09). This study also established that the number of the off-label medicines used significantly increased the hazard of ADRs (HR 1.28, 95% CI 0.43-3.78, $p=0.002$) (Saiyed *et al*., 2015). Diabetes mellitus was most significantly associated (OR 3.57, 95% CI; 1.11-11.49, $p=0.032$) with the development

of ADRs in a study conducted in patients receiving Directly Observed Treatment Strategy (DOTS) for tuberculosis (Siddiqui *et al*., 2016). Drug discontinuation due to ADR is common. ADRs related to disease-modifying anti-rheumatic drugs (DMARD) withdrawal was observed in 2/5 (13.3%), 9/116 (7.8%), 6/185 (3.2%), 3/131 (2.3%) and 8/444 (1.8%) of rheumatoid arthritis patients receiving leflunomide, methotrexate, sulphasalazine, chloroquine and hydroxychloroquine, respectively (Mittal *et al*., 2012).

Drug Classes and Adverse Drug Reactions

Acneiform eruptions (56) and tinea (41) were the most commonly observed cutaneous ADRs associated with topical/oral/inhaled corticosteroids (n=100) in cross-sectional study in dermatology outdoor patients (Kannan *et al*., 2015). In a retrospective study, most common antibiotics resulting in ADR were inj. ceftriaxone [140 (35.71%)] and tab. azithromycin [29 (7.39%)] out of 392 ADR events reported to antimicrobials. This study also observed dermatological [186 (47.4%)] and gastrointestinal [154 (39.3%)] systems as the most common organ class affected due to antibiotics associated ADRs, and higher rate of type A [255 (65.1%)] ADRs due to antibiotics (Richa *et al*., 2015). In a prospective observational study, physical and psychological domain scores of WHO Quality of Life BREF decreased at three months compared to the baseline in hospital outdoor patients receiving antipsychotic therapy who experienced ADEs. Risperidone (10) and olanzapine (8) were commonly associated with ADEs in this study (Chawla and Kumar, 2017).

Constipation, nausea, vomiting, alopecia and hematological changes were the commonly encountered ADRs due to cancer chemotherapy in a tertiary care teaching hospital with cisplatin, cyclophosphamide, paclitaxel and 5-flurouracil as the most commonly suspected chemotherapeutic agents for ADRs (Wahlang *et al*., 2017). Prevalence of ADR in patients receiving taxanes and vinca alkaloids was 11.8% with paclitaxel (54.6%) and vincristine (39.2%) as most commonly attributed drugs for ADRs out of 97 ADRs reported among 488 patients on microtubule-damaging anticancer drugs. Gastrointestinal system [39 (40.2%)] was the most affected organ class due to ADR followed by the bone marrow [32 (33%)] and the skin [8 (8.2%)] in these patients (Manohar *et al*., 2016).

Medication Errors

Medication error rate for hospital in-patients and out-patients was found to be 22.4% and 11.4%, respectively in a combined retrospective and prospective study aimed to guide rational use of medicines for therapeutic benefits and enhanced compliance. The researchers in this study considered acceptable error rate 3% as standard. Medication errors are preventable and this research emphasized the need to establish a medication error disclosure and prevention system (Thakur *et al*., 2013). Three important types of medication errors namely prescription, transcription and administration errors were assessed for frequency and nature in a cross-sectional study. In 500 cancer out-patient observations included in this study, medication errors were observed on 41.6% patients and among these, prescription errors, transcribing errors, and administration errors accounted for 114 (54.8%), 51 (24.5%) and 43 (20.7%), respectively. Considering the potential medication related harm associated with medication errors, this study highlighted the need to establish a blame free error reporting system. The researchers opined that computerized prescriptions, periodically training healthcare professionals regarding patient safety, and quality patient care could reduce the medication error rate (Mathaiyan *et al*., 2016).

Pharmacovigilance System

Increasing pharmacovigilance awareness was observed in a cross-sectional survey conducted in a tertiary care teaching hospital. An overwhelming [84 (93.3%)] response was received to the questionnaires in this study with 64.3% of respondent aware of pharmacovigilance. The researchers involved in this study concluded that the curriculum in academic programs focused at Pharmacovigilance will be helpful in improving ADR reporting rate (Pimpalkhute *et al*., 2012). The quality of ADR reporting can be improved by education and training of healthcare professionals. All respondents (80) to a survey in a tertiary care teaching hospital in Pune expressed the need for proper training to clinicians regarding ADR reporting system. Majority of these respondents (81%) in this survey felt that the reporting should be made mandatory. An interventional lecture in this study

enhanced (96%) the knowledge regarding ADR reporting system (Sanghavi *et al*., 2013).

A pharmacologist stated that: "we largely rely on the ADR data from other countries as we do not have our own national ADR database despite the country having one of the largest ophthalmic patient populations worldwide". The researcher hopes that suspecting ADR during diagnosis must become an integral part of clinical practice and reporting of ADR will become popular with the newly introduced PvPI (Dubey and Handu, 2013). Only 22.7% of postgraduate student respondents to a Knowledge Attitude and Practice (KAP) questionnaire survey in a medical college in Bihar were aware of PvPI. But 93.9% of the respondents had encountered an ADR during their clinical practice (Panja *et al*., 2015). In another qualitative KAP study, all the participants (42 medical faculty/residents and 89 nursing staff) knew about the ADR awareness programme, meaning of ADR, and they firmly believed that ADRs should be reported. Participants also admitted that forgetfulness and workload are the major constraints for not reporting ADRs (Gajjar *et al*., 2017).

Spontaneous ADR reporting forms usually expect to furnish information regarding approximately 25 data elements. A cross-sectional observation study that compared CDSCO ADR reporting form, yellow card, MedWatch and blue form for contents and quality found that nurses take longer time to fill ADR reporting forms compared to doctors and pharmacists, and majority healthcare professionals missed to complete reporter's information. Though the CDSCO ADR reporting form mentions 'Your 5 minutes can help us ensure safer medication', this study found that the healthcare professionals need at least about 11 minutes to complete the form (Rehan *et al*., 2014). Under-reporting of ADR is an ongoing concern in spontaneous reporting system. A cross-sectional prospective questionnaire-based analysis found that lack of knowledge and awareness regarding PvPI, lethargy, indifference, insecurity, complacency, workload, lack of training were the common reasons for under-reporting. Also, the study found that ADR reporting by postgraduate students was influenced by major academic activities, exams, thesis and the synopsis submission time. The researchers underscored the need for multipronged approach to overcome under-reporting in PvPI (Tandon *et al*., 2015).

Antibiotic resistance is a significant burden in the healthcare. Several microbes that may turn out to be resistant to one or more antimicrobial agents is a major challenge in quantifying antimicrobial resistance. In a review of pharmacovigilance initiatives associated with antimicrobial resistance, the researchers felt that antimicrobial resistance will definitely reduce if the global action plan initiated by WHO by means of WHONET software programme is implemented successfully. Also, the review detailed that harmonized definitions, information deficit from developing countries and lacking clinical outcome data, inadequate microbial testing facilities, insufficient funding, political constraints are some of the problems in Pharmacovigilance related to anti-microbial resistance (Bairy *et al*., 2016).

Other Studies Related to Adverse Drug Reactions

To compare and evaluate the risk of nimesulide in India and EU for regulatory action, data on nimesulide from EU available from EMA website and Indian data from published literature, WHO VigiBase and International Medicines Statistics (IMS) was reviewed. Authors in this study concluded that limited and varying data in post-marketing studies on ADRs and drug utilization for nimesulide from India made regulatory decision difficult (Kshirsagar and Bachhav, 2013).

The total cost to a tertiary care teaching hospital due to ADRs in 6 months was identified to be Rs. 1,567,397 (US$ 36,451). This study included 317 ADRs in 246 patients. The average cost per patient hospitalized with an ADR was Rs. 4,945 (US$ 115). Considering the per capita annual expenditure on health in India (US$ 109), the cost per ADR was found to be higher compared to developed countries (Rajakannan *et al*., 2012).

A retrospective, record-based study from Bihar reported incidence of ADR as 0.67 per thousand patients. Department of skin and venereal diseases (33.2%) and department of oncology (18.8%) reported maximum number of ADRs in this study with antibiotics and anticancer drugs as commonly implicated for ADRs (Pathak *et al*., 2016). Anti-tubercular drugs (34.4%) and anti-retroviral agents (76, 20.3%) were the most commonly attributed drug

class for serious ADR in a retrospective analysis reported from Gujarat. Of all ADR reported in this study, 12.6% were serious in nature with 43.7% requiring intervention to prevent permanent impairment or damage and 42.1% ADR necessitating hospitalization (Prajapati *et al.*, 2016). ADRs identified in a prospective observational study were categorized as possible (40.1%), moderate in severity (30.6%) and not preventable (27.9%) (Remesh *et al*., 2014).

Geriatric population (54%) accounted for maximum drug induced diseases (DID) followed by adult (37.8%) and paediatric (8.2%) in a retrospective cross-sectional study. Anti-tubercular treatment, anti-retroviral treatment, ceftriaxone injection, steroids, NSAIDs, anti-microbials and anti-cancer drugs were found as commonly offending drugs in DID in this study with gastritis [177 (7.4%)] as the most commonly identified DID followed by diarrhoea [141 (5.9%)] and anaemia [114 (4.8%)] out of 924 DID identified (Tandon *et al*., 2015).

Discussion

There is a lack of specialized university certified academic courses in Pharmacovigilance limiting the ability to build skills and capacity further confining research in Pharmacovigilance. This study included only the Pharmacovigilance research published by Pharmacologists. Research in this area in India could be wide-ranging considering research done by Clinical Pharmacists in Pharmacy Practice, other healthcare professionals and pharmaceutical industry. Established Pharmacovigilance methodologies like sentinel sites, drug event monitoring, registries, case control studies, cohort studies and targeted clinical investigation were not encompassed by studies included in this review (International Councilon Harmonisation). There is scope for applying tools like Anatomical Therapeutic Chemical (ATC) classification of drugs, Medical Dictionary for Regulatory Activities (MedDRA) or WHO Adverse Reaction Terminology, Defined Daily Dose (DDD), WHO Causality Assessment in Pharmacovigilance studies.

Majority of the studies included patients from hospital settings predominantly from tertiary care centres. Considering large volume of medication use in the community, Pharmacovigilance research focused on community settings should be earnestly fostered. Nearly all studies were carried out in a single centre. There is an important need for networking of Pharmacovigilance researchers towards multicentre studies with harmonized methodology. There were many studies on cutaneous ADRs. Similar emphasis by researchers on other system organ classes can elucidate true burden of ADRs. Studies were concentrated on ADRs. Research involving all aspects of drug related problems would help achieve the overall objective of Pharmacovigilance. Lot of research done remains unpublished and hence the researchers should be inspired to bring out all of their research work towards publications.

Most of the studies were self-funded. The PvPI should identify areas of research interest that is relevant to our country and fund the research. Research funding should also be supported by other government organisations and pharmaceutical industry. The PvPI should give extra emphasis to risk assessment and management utilizing the strengths of Adverse Reaction Monitoring Centres (AMCs) within its network and in collaboration with the pharmaceutical industry. PvPI initiatives along with recently established WHO collaborating centre should develop research capacity in public health programmes.

The Pharmcovigilantes in India should also consider developing the expertise and expand their work to monitor drug induced adverse birth outcomes (Pregnancy Registry), adverse events following immunisation (Vaccine Safety Surveillance), safety monitoring of blood & blood products (Haemovigilance), monitoring of medical devices (Materiovigilance). Such research activities will strengthen the Govt. of India initiatives in respective areas with the ultimate goal of ensuring patient safety.

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