Indian College of Physicians (ICP) Position Statement on Pharmacovigilance

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Abstract
Pharmacovigilance is the art and science of detection, understanding and prevention of adverse drug reactions and not merely a critical analysis of prescriptions and errors. This field starts with reporting by clinicians of a suspected adverse drug reaction (ADR) to the pharmacologist followed by joint causality analysis and ends at the application of new information by a clinician for benefit of patients. There are a number of ways, which can be utilised for reporting adverse effects using pen and paper format to software applications for smart phones. Varied types of activities spreading from systematic reviews to the mechanistic evaluation of ADR can be performed under the umbrella of pharmacovigilance. It is of utmost importance for clinicians to understand how to identify, communicate and understand adverse effects of drugs with an aim to prevent harm to patients.

Executive Summary
Pharmacovigilance is defined as the art and science of detection, assessment, understanding and prevention of adverse drug reactions or any other drug related problem. It is one of the least understood and lesser practised dimensions of medicine. A number of recent changes in regulations with regard to drugs (e.g. pioglitazone) and fixed-dose combinations (FDCs) have highlighted the role of this field in practice of medicine.

Pharmacovigilance aims at improving patient safety, by generating drug safety data from clinicians using them in diverse subsets of patients. The chronic use of medicines in such a heterogeneous patient population shows many adverse effects, which require analysis. The reporting of all these adverse effects by practising clinicians and their analysis by a team of clinicians and pharmacologists help in understanding the various aspects of drug safety. Communication of safety signals among clinicians modifies prescribing patterns and improves patient safety. Thus, pharmacovigilance begins with clinicians, with reporting of Adverse Drug Reactions (ADR), and ends at clinicians who use the data for improving patient safety.

Pharmacovigilance can be practised by spontaneous reporting of ADR, writing a narrative or systematic reviews on drug safety, undertaking research into mechanisms of ADR and conducting clinical trials for safety analysis.

Office of Central Drug Safety and Control Organisation (CDSCO) periodically publishes specific drug related adverse reactions to be noted. All physicians should remain vigilant about safety alerts from the national organisation.

Causality assessment of ADR establishes a relationship between suspected finding and drug use. This process is never complete without inputs and assessment by a practising physician. Scoring scales are used to assign causality category to the suspected finding. Practising physicians are expected...
to be conversant with principles of causality assessment of ADR.

Pharmacovigilance and its principles hold an important place in contemporary clinical practice. This subject improves patient safety, generates evidence refuting the use of a drug of interest or use a drug with precautions, and thus contributes to clinical therapeutics. The Indian College of Physicians supports the integration of pharmacovigilance in daily clinical practice and medical research. This position statement encourages physicians to remain pharmacovigilant and facilitates this practice.

**Preamble**

Pharmacovigilance has traditionally been considered as the practice of monitoring prescriptions for adverse effects of drugs and medication errors. Though it is considered by some clinicians to be critical of their activities and capabilities, the program is intended at improving patient safety and treatment outcomes while improving the level of trust between physician and patient.

Pharmacovigilance is a relatively new dimension of medicine which focusses on the use of epidemiological and research techniques to understand and prevent adverse effects of drugs. This dimension was not part of teaching curriculum of medical sciences a few years back. Recently due to many drug withdrawals from the market and growing concerns regarding patient safety among the general public and drug regulators, the interest in this field has gone up.

World Health Organisation defines Pharmacovigilance as “the art and science of detection, assessment, understanding and prevention of adverse drug reactions or any other drug related problem.” This definition describes the scope of this activity which extends from detection and reporting of ADR and to data analysis to information sharing with health care providers for prevention of adverse outcomes related to drug use. It encompasses the whole gamut of activities surrounding the safety aspects of drug use.

The increase in chronic morbidity has meant an increase in drug use. There has been an increase in a number of drugs, fixed-dose combinations and polypharmacy. Hence Indian College of Physicians has brought out this multi-disciplinary position statement on Pharmacovigilance.

**Scope of Pharmacovigilance**

As discussed above, a variety of activities can be taken up under the umbrella of pharmacovigilance. The profile of activities routinely done are detection and reporting of ADR, data entry in software (VIGIFLOW), data analysis at the local, national and global level, signal generation and communication of newly detected adverse outcomes to health care providers through various channels. The profile of activities begins with clinicians/health care providers and concludes with them receiving new information intended to improve patient outcomes. This process involves the use of a number of epidemiological and research tools and mass communication skills. Pharmacovigilance is a self-sustaining process which starts with clinicians and ends at clinicians.

**Practicing Pharmacovigilance**

The practice of pharmacovigilance and allied activities by clinicians is an area which suffers from a lack of clarity and vision. We propose a simple operational framework to enhance understanding. Any action aimed at individual or epidemiological for improving patient safety, whether associated with the use of drugs or devices, detection or communication is the practice of pharmacovigilance. Practising physicians are concerned about patient safety but are dependent on the interpretation of facts taught during the teaching of the medical curriculum. Pharmacovigilance helps them internalise these facts and utilise them in daily practice.

1. **Spontaneous Reporting:** Understanding epidemiology of adverse drug reactions begins by identification of ADR. Reporting ADR to nearest ADR Monitoring Centre or by calling up the telephonic helpline of Pharmacovigilance Program of India (PvPI) at toll-free number 1800-180-3024 is the next step in the process. Filling up of ADR reporting form can be done by staff trained in
reporting of ADR or by Patient Safety-Pharmacovigilance Associates (PSPvAs). Indian Pharmacopeia Commission, the organisation responsible for running and managing Pharmacovigilance Program of India has recently launched an application for smartphones dedicated to reporting of ADR by clinicians.2

Maintaining Registries: Maintaining a registry of sub-groups of patients according to diagnosis e.g. hypertension or therapeutic areas e.g. biologicals or any other sub-group can be of help in identification of drug-related problems e.g. hypersensitivity and other immunological reactions to biological agents. The first indication regarding the probable association of use of pioglitazone with bladder carcinoma came from analysis of data from a registry of type 2 diabetic patients. This is easily possible with the use of computers with software for the patient management system.

2. Narrative or Systematic Reviews: Academically oriented clinicians can work on safety aspects of therapy by writing a narrative or systematic reviews or conducting a meta-analysis. This is routinely practised in the developed world and has contributed to a great deal in drug withdrawals. Special training in statistics is required for such kind of work and activities. Drug regulators across the globe depend on such work for their decisions on labelling and availability of the drug in the market.

3. Original Mechanistic Research: Mechanistic modulation of ADR either at the level of the individual or molecular level is also the practice of pharmacovigilance. The gamut of activities does not stop at reporting and generating signals only. It goes on until a solution to drug-related problem is found. Mechanistic evaluation can be done by pharmacological manipulation of ADR like in the case of use of proton pump inhibitors (PPIs) with non-steroidal anti-inflammatory drugs like ibuprofen for prevention of gastric symptoms. Additional investigations are required to understand the pathophysiology of ADR. Such studies are usually possible in academic institutes which have required infrastructure for molecular level research.

4. Original Clinical Research: Clinical trials conducted for comparing the safety of two drugs or for evaluation of proposed new solutions also fall under this category. Any such activity will require a lot of time of practising physician and resources dedicated to trial related activity. Additionally, with increasingly complicated and aggressive regulatory environment for clinical trials, this may not be feasible in many small clinics or nursing homes. However, in academic institutions, all these activities can be conducted with vigour. A number of other activities that can be easily undertaken by community health specialists for communicating the adverse effect of drugs and curbing self-medication based on the distorted and incomplete information.

Drugs of Interest for Safety Related Issues

Pharmacovigilance Program of India has released the list of drugs and specific ADR which are being monitored aggressively and has urged all clinicians to remain vigilant about them.3 The list is given in Table 1.

It must be noted that actions of these drugs and adverse effects span the entire spectrum of internal medicine and no system is immune.

Causality Assessment and Role of Clinicians

Assessment of causal association between a suspected event and drug use is a scientific process requiring medical and pharmacological input to rule out the possibility of the event being a manifestation of underlying pathology and manifestation of the disease process. Standard scales are available which assign a category (Definite, probable, possible, unlikely etc.) to the probability of an event being due to drug use and not due to other causes. A classic situation where causality assessment can play an important role is in cases suffering from drug fever where pyrexia can be either because of drug use or infectious in origin.

This kind of work requires intensive inputs from clinicians and is a team work before any change in labelling is proposed. The most recent example of such an activity leading to regulatory U-turn in India is the use of pioglitazone for the management of type 2 diabetes mellitus.4

It is expected that practising clinicians familiarise themselves with the process of differentiating the causality of suspected event being from drug use or disease process or some other unexplained confounding factor. Such knowledge will be helpful in better patient management by timely interventions in terms of use of drugs for managing an event or not an unnecessarily withdrawing suspect but effective drug.

Importance of Vigilance

Detection of adverse effects of drugs manifesting after long-term treatment e.g. urinary bladder carcinoma with pioglitazone, emphasises the role of continuous monitoring of patients for adverse outcomes. Additionally,
with the launch of new drugs for management of a variety of diseases like SGLT-2 inhibitors and DPP-4 inhibitors for type 2 diabetes mellitus etc. and lack of information following chronic use in a variety of population, being vigilant about any suspected adverse medical outcome becomes necessary. In patients with compromised renal, hepatic or cardiac functions, it is required to modify doses for minimising adverse effects. The process of approval of drugs in India presently relies a lot on the clinical trials done in the western world. Racial and ethnic factors make us different from other parts of the world. A drug safety database of India is the unmet medical need of the hour and clinicians can only help in creating such a database, which will be of immense help to drug regulators in enhancing patient safety. Through this position statement, Indian College of Physicians hopes to facilitate such activities.

**Summary**

Table 2 summarizes issues related to pharmacovigilance.

### Conclusion

The practice of Pharmacovigilance aims to create a system where all ADR (ideally) are reported and drug-related problems taken care of scientifically using evidence-based-medicine. Presently there is a big gap between practice and achieving desired goals and a lot needs to be done in this field. Apprehensions of physicians need to be taken care of and ways need to be discussed for making this activity to bring out the desired outcomes.

### References