

Pharmacovigilance and spontaneous adverse drug reaction reporting: Challenges and opportunities

Although the strategies in controlled clinical trials are to identify the safety and the risk associated with the use of medicines, it does not reflect the way the medicines are used in real life practice. Therefore, the postmarketing safety monitoring of medicines through pharmacovigilance (PV) system is essential and continues throughout the marketed life of medicines. The recent pandemic has been a good example to highlight the importance of the safety monitoring of medicines and vaccines during public health emergency. The accelerated approval of “repurposed” medicines for COVID-19 and “compassionate use” of bedaquiline for drug-resistant TB has proved the crucial role of PV to support regulatory decisions and ensure patients’ safety.

Spontaneous reporting of suspected adverse drug reactions (ADRs) by the health-care professionals (HCPs) and pharmaceutical companies is the cornerstone of national PV system, albeit it is voluntary as point of patient care. The foundation of spontaneous ADR reporting system relies on professional obligation, initiative, motivation and contribution by HCPs. Unfortunately, it has been compromised and suffers from underreporting.^[1,2] As a matter of fact, underreporting is a universal phenomenon, though the extent may vary from resource-limited to resource-intensive countries. It has been estimated that only 5%–10% of ADRs are reported.^[3] The availability of extensive literature, systematic reviews, and research articles on PV and ADR reporting provides evidence that underreporting has been widespread globally.

In this issue of the journal, Panneerselvam *et al.* evaluated knowledge, attitude, and practice of PV among postgraduates during educational intervention.^[4] Interestingly, the authors observed that participants already had good theoretical knowledge about PV preintervention; nevertheless, their attitude and practice significantly improved postintervention. It is a well-known fact that educational interventions are effective tools to sensitize, increase awareness, and educate the participants. However, it is more important to know whether the improvement in attitude and practice on ADR reporting changed the behavior in real life practice. Unfortunately, it has been

experienced and documented that postintervention, the reporting declines over a period of time.^[5] Various measures have been adopted to improve reporting such as training to HCPs, simplifying reporting by online tool and mobile app, communicate safety concerns, regular feedback to ADR monitoring centers (AMCs) etc. However, the challenge of underreporting of ADRs continues. Let us introspect the issue from PV program and HCPs perspectives.

The National PV Programme of India (PvPI) has been fully functional with currently more than 500 AMCs to collect, collate, and analyze safety reports of medicines, vaccines, medical devices, and blood products to determine the causality, identify signals, communicate safety alerts to HCPs and recommend subsequent actions to regulatory authorities, if any. In spite of large number of AMCs, very few (majority being public sector and tertiary care centers) are functional and contributing actively. This calls for performance assessment of each AMC along with situation analysis for lack of contribution. Second, to complement the spontaneous reporting, the PV system has been integrated with other national health and immunization programs. In addition, the national coordination center provides periodic skill development and technical training to personnel engaged in PV activity and support AMCs to organize training for HCPs for capacity building. The system has been supported by government and regulatory authorities by introduction of PV guidelines for marketing authorization holders for pharmaceutical products. The regulatory decisions are also reflected in WHO newsletters and communicated to stakeholders. Moreover, PV is a part of medical and pharmacy curriculum and is mandatory for pharmaceutical industry. Each medical institution is mandated to have a PV committee, making PV an institutional activity. Even patients and end users are empowered to report ADRs. A helpline and reporting forms in all local languages are available. Further, ADR reporting has been initiated for accreditation of hospitals by NABH standards. The ADR reporting base is wide, easily approachable, and known to all like any other health program as observed by Panneerselvam *et al.*^[4] Thus, the PV system is well established and has sustained its activities in the last two decades. India’s contribution to international

database has substantially increased over the years with 0.75 out of 1 quality score (National Coordination Centre, PvPI). However, in view of large patient population, vast ethnic variability, disease burden, practice of different systems of medicines, and wide variety of novel medicines produced and available in the Indian market, it is still low and there is a scope of further improvement.

On the other hand, HCPs have several personal and professional reasons for underreporting. The outpatient departments (OPDs) are too crowded, the prescribers are too busy and may have diverse clinical priorities, non-serious or already known ADR, uncertainty of causal association between a medicine and ADR, non-availability of separate space or room to report and filling up the suspected ADR form and there is no apparent benefit for the time and efforts. Based on the author's experience of running AMC as former regional coordinator, the substantial contribution to ADR reporting is from dedicated pharmacology department faculties, postgraduates, and few academically oriented and research-minded clinicians. In fact, the location of AMC at pharmacology department creates a false perception among prescribers that ADR reporting is a domain of pharmacologists. Most of the ADRs reported from teaching hospitals are collected by students during their ward and OPD visits and hence are either "semi-spontaneous or solicited reports" rather than "spontaneous reports." While the contribution from private sector HCPs, district hospitals and professional organizations has been negligible so far. The mission to expand avenues to increase the reporting of suspected ADRs includes engagement and education of HCPs, collaboration among stakeholders and exploring electronic technology.

Engaging enthusiastic HCPs by regular feedback, personal communication, and scientific meetings would help build the trust and strengthen the reporting system. Acknowledging and appreciating their contribution by credits, award, inviting as faculty or guest speaker to share their knowledge and experience would encourage other HCPs to report ADRs. Engaging them as coinvestigators, coauthors for all ADR-related projects and publications would prove that PV and ADR reporting are a collaborative institutional activity. Persistent efforts will strengthen the trust and relationship with clinical departments, bridge the gap between nonclinical and clinical discipline, and will gradually make ADR reporting as a medical need. Communicating the safety alerts to prescribers by text messages, newsletters, and uploading information on institute website would improve awareness and patient care. In addition, engaging professional medical

associations, prescribers, and marketing authorization holders for targeted spontaneous reporting (TSR) of newly introduced or controversial medicines would help signal detection, e.g. TSR of monoclonal antibodies by medical oncologists, rheumatologists, and pulmonologists or drug-induced liver injury by gastroenterologists, etc. Moreover, engaging consumer organization, extending the program to non-teaching private hospitals, primary and secondary care health centers and private practitioners would widen the scope of PV reporting. Training clinical research associates to collect ADRs, which could be validated by HCPs, would enhance ADR reporting in private sector.

Multiple educational interventions and periodic reinforcement along with reminders can have long-term impact on ADR reporting than single intervention. The training program should be multifaceted, multidisciplinary, and interactive with sessions on group dynamics and hands-on training. A robust training involving all levels of health care focusing on real-world case scenarios of safety, multiple simultaneous drug administration, medication errors, etc. will update HCPs on PV and significance of ADR reporting.

Besides quantity, the quality is critical for a meaningful assessment of individual case safety reports. Efforts should focus on quality and completeness of data. The performance of each AMC should be measured not only by number of reports submitted but also completeness score determining authentic reports with causality assessment and description of case narratives. Each AMC should have an in-house system to check the quality of reports before submitting to national center. Frequent PV training will help in this regard.

If persistent efforts are not sufficient to change the behavior, it is time to think unconventional methods for the benefit of patients and community. The multimedia campaign and social marketing concept has been successfully adopted for health education. Similarly, ADR reporting awareness could be spread through TV, radio, newspapers, posters, display hoarding at community pharmacies, public transport system, clinics, and hospitals. While disease registry and patient registry for systematic collection of data in real world are not new, the concept can be used for post approval adverse event reporting for certain therapeutic groups by structured collaboration between HCPs, professional organizations, and pharmaceutical companies. Interestingly, the social media sites have been proposed as an alternative PV tool for real time monitoring of ADRs and expedited signal detection.^[6,7] These alternative PV

tools seems to be exciting; however, there are several questions such as variations in drug names, reaction terms, and treatment taken to assess causality that need to be addressed.

Considering the increasing use of electronic technologies in health care, its integration with traditional PV offers opportunities to enhance and facilitate safety surveillance. Electronic health records provide large databases to identify important safety data that are serious with public health impact, characterize the risk factors and adds value to benefit- risk assessment of medical products in real world. Resource intensive countries with robust regulatory system analyze such databases for safety assessment of approved medical products.^[8] Databases also offer an opportunity to apply artificial intelligence techniques to leverage PV core activity by prompt accurate decision-making. The modern PV tools seem to be exciting and ambitious; however, in view of fragmented health-care system in India and different administrative arrangements, its implementation is another challenge.

While the PV system has made substantial progress in last decade, the challenge of underreporting is universal and continues. There is no magic pill to engage HCPs for proactive contribution and spontaneous reporting of ADRs. Multiple educational interventions, engagement of HCPs and collaboration of stakeholders would go a long way in changing the attitude and behavior related to ADR reporting. Electronic health records and databases have the potential to identify early drug safety issues, however, cannot replace spontaneous reporting, the core data generating method of traditional PV system. Each approach, organization, and level of health-care system has limitations, issues, and challenges. What really matters is “*reporting culture*” and “*proactive approach*” for spontaneous reporting and a strong PV system to ensure medicine safety.

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