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An Overview of Spontaneous Reporting, Targeted Spontaneous Reporting and Cohort Event Monitoring-Pharmacovigilance Methods: Myths and Facts

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Abstract

Adverse drug reaction (ADR) reporting is an important safety concern to monitor safety among the patient. Pharmacovigilance (PV) is usually involves in detection of spontaneous adverse reaction, therefore these shall be submitted to the National Coordination Centre Pharmacovigilance programme of India (NCC-PVPI) which is located at Ghaziabad functioning under ministry of health and family welfare, Government of India. ADR is a global concern that causes serious impact on consumers both in terms of health and financial aspects. Hence monitoring of these adverse reactions is utmost important attribute to enhance patient safety. Perhaps, India is adopting spontaneous reporting (SR) system since 1998, henceforth targeted spontaneous reporting (TSR) system came into consideration in 2010, and that is a complimentary method to spontaneous reporting. This system is useful to establish evidence-based reports generation of specific drug and ADR combination, increase alertness and also helpful in recognizing harmful risks The main aim of this article is to encourage evidence-based decision making to enhance patient safety. In addition to this, establish a functional reporting system i.e. targeted spontaneous reporting system to monitor the safety of targeted medicines and to learn more about the safety profile of new medicines in the early post marketing phase in our population.

Keywords: Adverse drug reaction, Pharmacovigilance, Spontaneous reporting system, Targeted spontaneous reporting and cohort event monitoring.

BACKGROUND

An adverse drug reaction (ADRs) affects the majority of population under medications worldwide. ADRs cause significant change in morbidity and mortality, and may increase the economic burden on the healthcare system. As per World Health Organization (WHO), Pharmacovigilance (PV) is defined as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects and all other problems related to medicines.[1] Passive surveillance/voluntary reporting of spontaneous adverse events from healthcare providers (HCPs and consumers following the administration of a pharmaceutical product have been usually adopted to monitor the product safety. Various reporting systems have been adopted in different countries to report ADR's to National Pv centre, such as cohort event monitoring system and spontaneous report monitoring system (also known as stimulated, enhanced, and targeted). These methods are significant to identify the quantitative aspects of drug safety, to better recognize high-exposure groups and specific risk factors, to distinguish ADRs related with particular medications and in a cohort of patients. Cohort event monitoring (CME) system is one of the oldest methods of reporting ADR's. Targeted spontaneous Reporting (TSR) is an innovative technique of PV system that harmonizes findings of conventional safety monitoring systems. The newly established method TSR system frames on spontaneous reporting system by accumulating features of CME, therefore which interns useful in establishing an economical model of collecting information on suspected ADR's. This method is implemented for the identification of ADRs in clinical practice on which minimal data already existed with PV system, which requires investigation on existing spontaneous reports. Additionally it covers the reactions occurring from drug-drug interactions or drug related effects among high risk populations to improve the understanding of the potential risks as well as to provide a support for adequate management of patients and supervision of medications, furthermore helpful in consequent changes in clinical practice.

National Pharmacovigilance Programme mainly relies on the voluntary reporting or spontaneous reporting from various stakeholders.[2] The major source of information mainly obtained from spontaneous reporting systems.[3] The drug safety reports helpful in identifying safety alerts and to monitor rational use of medicines in public.[4] Identification of signals at early stage results in preventing potential risk, further collateral research, regulatory decision and updating product safety information[5-6]

Methods of Pharmacovigilance Systems

Spontaneous reporting system (SR)[2,6]

This is the widely adopted system of PV which is often referred to as "voluntary" reporting. Spontaneous reporting depends on the reporters being educated and motivated to record and submit their observations. Training should be given to all the practicing healthcare professionals and members of the community in sensitizing the reporting culture in terms

of what, where, when, how, and whom to report an adverse reactions. Subsequent training shall be given to adopt techniques to overcome the identified limitations of spontaneous reporting especially the under-reporting.[8] This system has its own merits in supporting reports from authentic clinical practice in contrast to clinical trials, in which susceptible population is excluded; also the duration of treatment is limited. Nonetheless, this system has a number of demerits such as under-reporting being the major one[9-10] it only provides a numerator; and also lack of information on population exposed to the drug. Hence, it is complex to quantify the risk associated with a suspected drug accurately. Moreover, the reported cases are also subjected to reporting bias. Other limitations include variation in the quality of reported details submitted and the missing information. In spite of all these drawbacks still spontaneous reporting is the cornerstone of PV, because it allows to prompt detection of probable safety alerts associated to drugs' use through the early detection of new ADRs in low frequencies. The voluntary reporting is the only basis of SR, as underreporting is major concern which is due to poor motivation of healthcare professionals. Hence it is difficult to find out the actual incidence of ADRs with respect to particular medication. Short term and long term toxicity data plays an important aspect in communicating the distinct therapy in the management of patients suffering with certain disease conditions.[11–13] It is crucial to assess and distinguish the risk associated with treatment, also reduce the harm, increase better patient compliance and not to mention to sustain public belief in the programme.[14] Although SR remains the basis of drug safety monitoring, alternative surveillance systems are necessary to assess the prevalence and severity of both expected and unexpected adverse reactions develops in long-term treatment exposed population.[7] Active PV method is essential to monitor safety of all medications, to improve patient safety and wellbeing.[15]

Cohort Event Monitoring (CEM)

Cohort Event Monitoring (CEM)[16-17] is a form of active PV system primarily developed for certain focused drugs for prospective, observational study of adverse events encountered with specific drugs. A CEM programme is primarily essential for the investigation of a distinct medicine in day-to-day clinical practice, in addition to this it is not only useful in early phase IV clinical trials, but can also helpful in identifying the risk asscociated with marketed medications. It is hinge on the standards of the New Zealand intensive medicines monitoring programme[18] and the UK prescription event monitoring[19] other than that in most limited support countries. Thus, CEM is an early warning system that record group of patient's clinical events on a specific therapy, for capturing all clinical events associated medicine of interest used in Public Health Programmes (PHP). Accurate assessment shall be done to the patients prior to initiation of treatment followed by after initiation of treatment. It accounts utter events pertaining to medication, regardless of whether or not the drug is responsible for the event. CEM involves recording all events with following data; Any new medical events (alteration in medical aspects, strange symptoms or diagnoses, or any alteration in laboratory investigations) that have observed during defined time interval prior to treatment initiation are also recorded. Follow up shall be taken after a definite time interval for the clinical investigation to consider any unknown adverse events that observed following the therapy initiation.

To document events occurred to patients during a control period, before and after initiation of study, treatment review forms are used. The length of study might be unlike it could not varied beyond the patient's expectations. A control line is generated from the events occurred during therapy in comparison to the events collected before the study initiation. Special ethical considerations are involved in CEM since it is only system that requires complete documentation of all clinical events along with follow-ups. As CEM mainly aims to find out the prevalence rate, hence important to refrain the duplicate entries; this can be achieved only if patients are recognised precisely. At the same time it is also essential to seek the approval from competent authority in the country as a requirement for collecting patient data. Many nations opt for informed consent from the patient (who experienced adverse event) however, this will be time consuming. The 'opt out principle' is an alternative to obtaining informed consent where details about the CEM programme is provided openly, and patients voluntarily can agree to part in programme for data collection as a measure of CEM. Also the method needs to endorse by the respective regulatory.[20]

Targeted Spontaneous Reporting (TSR)

The WHO proposes targeted spontaneous reporting (TSR) as a methodology that builds on the principles of spontaneous reporting and CME but enforced in a defined ambience.[21] In this method, specific group of patients are targeted to report specific safety concern due to suspected medicine. WHO developed TSR in 2010 and it is being piloted in the HIV treatment programmes in three countries (Kenya, Vietnam and Uganda). TSR may be chosen to record all suspected adverse reactions in the defined population or to target on particular adverse reactions of peculiar interest, for example treatment-threatening toxicity, etc. Aforementioned aids in limiting adverse events recording that are most important to patients and studies. Poor treatment adherence due to adverse events is also incorporated as one of the focused events in the TSR approach for reporting concern.

TSR creates a favorable circumstance to supervise all individuals under therapy, as part of medical care. Although, the willingness of HCPs to watch carefully in regard to targeted adverse reactions and subsequent reporting helps in to its rewarding pursuit. ADR reporting can be reinforcing by adopting distinct measures such as education, advocacy and mentoring.[22,23] Even though desperate from these purview, TSR, beside its focuses on targeted drug and ADR combinations, expected to possess a comparable beneficial results on reporting, further more shortened workload of healthcare professionals. Safety monitoring within a therapy group gives the denominator value of exposed patients, as a results we can establish the hindrance of events associated with medicines precisely. The objectives need to follow to meet TSR requirements are as:

- Careful monitoring for suspected adverse reactions associated with targeted drug in defined cohort treatment during normal medical care, and also encounters the medicine related problem.
- Tracing out the causal relationship between the target drug and triggered adverse event accomplished from ADR reporting form, same shall be documented in the patient records.
- A proper awareness shall be given to all HCPs involved in treatment to inquire adverse effects associated during therapy period.
- Same PV method along with reporting forms are used, specific training shall be given in case narrations and written procedures to support the study. Unlike the spontaneous reporting complete the reporting with

detailed information on Drug and ADR's.

- The primary concern of TSR is not only to identify the serious and life-threatening event/ ADR's but also finding out any suspected reaction. HCP's can be advised to report any adverse reactions associated with the medication.

- In contrast to CEM, patient interviews before and after the treatments is mandatory. Hence, less laborious, more feasible with limited financial resources. Thus, TSR enhance the quality of patient care by promoting the PV as a best practice.

DISCUSSION

ADRs are the fifth most common cause of hospitalization, deaths with an estimated burden of 197,000 deaths per year in EU.[24] In terms of the health of Indian population, it is necessary to have safety information on the medicines used in various public health programmes so that the maximum number of ADRs can be captured and the safety, efficacy can be established for the vary people.

The public health programmes targets the citizens of India. So these public health programmes acts as a lifeline for the vulnerable population and keeps a strict watch on each citizen's health. While providing the treatment this becomes a great platform for the healthcare providers to capture as maximum information as they can, so it could be used for further safety related issues and the therapy can be individualized. Well during clinical care to the public, healthcare providers can have a specific watch on diseases, medicines, age, geological conditions, food habits and many more confounding variables. This opens a doorway of getting maximum information on a single platform.

PHPs and PV can obtain shared benefits from each other; PV and ADR monitoring in PHPs can help in recognizing the rare adverse events and also risk factors in patients and can have overwhelming positive impact on the implementation and success of these programmes. PHPs at the same time can also provide an opportunity to introduce PV in countries that lack a system for drug safety monitoring.[25] Targeted reporting may have a positive effect on the ADR reporting. The drug safety alerts which are can be formulated and circulated by Pharmacovigilance Programme of India (PvPI) may increase the interest of healthcare providers which in turn elevate the rate of targeted reports and on that basis, the alerts can get strengthen and specific signals can be identified. But again it totally depends on the active participation of HCPs.[26]

The mainstay of signal detection process is usually has been spontaneous reports and now in many countries the PV system also relies on the reporting from literature resources to evaluate the benefit risk associations for some drugs. These scientific literatures may also impact the entire lifecycle of the drugs. Usually the healthcare professionals more often publish the case reports and case series but fails to report the same to the national pharmacovigilance centre.[27] In the country like India this has been the vary culture among the healthcare professions to usually publish such data on adverse drug reactions. But if it is not reported to the national pharmacovigilance centre then it may not have any significance for the general public.

This could be another attempt of targeted reporting that one can search for specific reactions which has been published but not reported. If such reports are getting reported to the NPC, this would certainly impact on the society directly by circulating the essential alerts to the HCPs and indirectly this collated safety information can help the national health programmes and can be considered while making the healthcare policies.

It has been made clear from the above comparison that spontaneous reporting system is a passive method of reporting ADRs that depends usually on voluntary reporting by the reporter and it is generally less expensive whereas CEM would be more costly than any of the other methods. Since all the ADR reporting is voluntary, many of the events go unnoticed and lead to underreporting, usually lacks in terms of quality and quantity, also have many biases.[28]

It becomes a moral responsibility of every healthcare provider and consumer to report adverse event encounter by him/her or during clinical practice to the national PV centre.[29]

Developing countries like India is doing good in the field of pharmacovigilance, and the efforts has also lead our country's national pharmacovigilance centre in implementing the Cohort Event Monitoring on the bedaquiline in the year 2016 and to become a WHO collaborating centre for Pharmacovigilance in regulatory services and public health programmes.[30] It is urging to implement targeted spontaneous reporting in terms of safety aspects.[31] Therefore robust PV system shall be adopted by implementing alternative system of reporting in India.

Countries adopting these three methods

In 1968, WHO Programme for International Drug Monitoring (WHO-PIDM) was started at Uppsala Monitoring Centre (UMC), Sweden with ten founder countries Australia, Canada, Czechoslovakia, Federal Republic of Germany, Ireland, Netherlands, New Zealand, Sweden, United Kingdom, USA and it was spread to 140 countries as full member countries and 30 associate member countries by 14th September 2020[32] and currently total 170 countries adopting this spontaneous reporting methodology over the world. VigiBase (International drug safety database) of the WHO-UMC holds over 20 million Individual Case Safety Reports (ICSRs) by May 2019.[33] WHO-UMC identifies drug safety signals from the reported suspected adverse drug effects (ICSRs) due to use of medicines by patients and started sharing on their website and also in WHO Pharmaceutical News Letters since 2012. WHO defined signal as "Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously. Usually more than a single report is required to generate a signal, depending on the seriousness of the event and the quality of the information".[34] The list of signals identified by WHO-UMC is presented in Table 1. Various countries conducted studies on TSR and CEM along with drugs are presented in Tables 2 and 3 respectively.

Table 1: List of drug safety signals identified by WHO-UMC.[35]

Sl. No	Signals	Sl. No	Signals	Sl. No	Signals
1	Abiraterone and Thrombocytopenia	41	Dronedarone and Polyneuropathy	81	Olanzapine and accidental drug intake by children
2	Aflibercept and deep vein thrombosis/pulmonary embolism	42	Edoxaban – Incorrect dose administered	82	Omalizumab and anaphylactic shock in females
3	Agomelatine and QT prolonged	43	Emtricitabine/Efavirenz/Tenofovir Disoproxil Fumarate and Phosphatase Alkaline Increased	83	Ondansetron and serotonin syndrome
4	Agomelatine and Increased Blood Pressure	44	Esomeprazole and gynaecomastia in obese adults	84	Pamidronic acid and Optic Neuritis
5	Agomelatine – Inappropriate schedule of drug administration	45	Etanercept and injection site ulceration / injection site necrosis	85	Parathyroid Hormone and Myocardial Ischaemia
6	Agomelatine and thrombocytopenia	46	Etanercept and ophthalmic herpes	86	Pazopanib and Pericardial Effusion
7	Agomelatine and Hypotension	47	Everolimus and serious gastrointestinal disorders	87	Phenprocoumon – Accidental overdose
8	Amitriptyline and dry eyes	48	Factor Xa inhibitors and haematospermia	88	Pregabalin and visual colour distortions
9	Artemether/Lumefantrine and Stevens-Johnson syndrome	49	Febuxostat and cardiac failure	89	Propylthiouracil and Stevens-Johnson syndrome, Erythema multiforme and Epidermal necrolysis
10	Atomoxetine and Dystonia in paediatric patients	50	Febuxostat and Hepatic failure	90	Prucalopride and Suicidal ideation
11	Atomoxetine and neutropenia in paediatric patients	51	Febuxostat and allergic vasculitis	91	Quetiapine and valproic acid interactions
12	Baclofen and Renal failure	52	Fesoterodine – GI haemorrhage	92	Ranolazine and Hallucination
13	Benznidazole and severe skin reactions	53	Finasteride and Convulsions	93	Roflumilast and Melaena
14	Brentuximab and Hepatic disorders	54	Fingolimod and T wave inversion	94	Roflumilast and pancreatitis
15	Brivudine and 5-fluorouracil – Persistence of a fatal drug-drug interaction	55	Fluoxetine and Deafness	95	Roflumilast and pneumonia
16	Ceftriaxone and Hepatitis in Patients 75 Years and Older	56	Ganciclovir and hypoglycaemia	96	rosuvastatin and ticagrelor -rhabdomyolysis
17	Chymotrypsin and anaphylactic shock	57	Ginkgo biloba L. and cardiac arrhythmias	97	Ruxolitinib and peripheral neuropathy
18	Ciprofloxacin, enalapril and acute kidney injury	58	Glibenclamide/glyburide and palpitations in the Asian population	98	Saxagliptin and Pancreatitis
9	Citalopram and Ramipril treatment - Hyponatraemia	59	Golimumab and Meningitis	99	Selegiline and hypoglycaemia in underweight adults
20	Clozapine – Drug dose titration not performed	60	Golimumab and Migraine	100	SGLT-2 inhibitors and genital pruritus
21	Colecalciferol and insomnia	61	Hexetidine and Severe hypersensitivity reactions	101	Complete loss of libido reported for women on systemic hormonal contraceptive
22	Combination products containing guaifenesin, paracetamol, and phenylephrine reported with severe upper abdominal pain	62	Ibrutinib and pneumonitis	102	Tapentadol and Aggressive reaction
23	Ibuprofen and Metamizole treatment - Acute renal failure	63	Ibuprofen and Erectile Dysfunction	103	Tapentadol and Delusion
24	Dabigatran and thromboembolism	64	Idelalisib and Leukoencephalopathy	104	Temozolomide and Oesophagitis
25	Deferasirox and pancreatitis in paediatric patients	65	Ivermectin and serious neurological events	105	Thiamazole and rhabdomyolysis
26	Denosumab and lichen planus	66	Lamivudine and hearing decreased	106	Tocilizumab – Psoriasis and Aggravated psoriasis
27	Denosumab and vasculitis	67	Levetiracetam and impaired renal function	107	Tramadol and hyperacusis
28	Desloratadine and the risk of experiencing dry eyes	68	Levofloxacin and myoclonus in the elderly over 75 years: susceptibilities and prescribing issues	108	Ustekinumab and Vasculitis
29	Desloratadine and aggressive reaction	69	Levonorgestrel-releasing intrauterine device and panic attacks: a signal raised in patient reporting	109	Vemurafenib and cardiac failure
30	Desloratadine and QT prolongation	70	Levonorgestrel-releasing intrauterine system products and suppressed lactation	110	Vemurafenib and Granulocytopenia
31	Desloratadine, loratadine and weight increase in children	71	Panic attacks with levothyroxine	111	Vemurafenib and renal failure
32	Desogestrel and night sweats, vulvovaginal dryness and dry eye	72	Linagliptin and Cardiac failure	112	Vemurafenib and Sepsis
33	Desogestrel and severe psychiatric disorders: panic attack, suicidal ideation and self-injurious behaviour	73	Metamizole – Documented hypersensitivity	113	Vemurafenib and Atrial fibrillation
34	Dextromethorphan and serious neurological disorders in children	74	Methotrexate – Incorrect drug administration rate	114	Vemurafenib and Pancreatitis
35	Dimenhydrinate and erythema multiforme/Stevens Johnson Syndrome	75	Methylphenidate and lockjaw	115	Vemurafenib and Thrombocytopenia
36	Donepezil – SSRI and SNRI – interaction and Serotonin syndrome	76	Midostaurin – photosensitivity reaction	116	Vemurafenib and Tumour lysis syndrome
37	Dronedarone and AV block	77	Mirtazapine and Rhabdomyolysis	117	Venlafaxine, pre-eclampsia, eclampsia and related disorders of pregnancy
38	Dronedarone, hyperthyroidism and decreased Thyroid Stimulating Hormone	78	Mometasone and Arrhythmia	118	Vortioxetine and aggression
39	Dronedarone and ventricular arrhythmia	79	Nintedanib and ischaemic colitis		
40	Dronedarone and vision abnormal	80	abdominal pain, chest pain and headache while using noscapine		

Table 2: Targeted Spontaneous Reporting: Various countries conducted studies on TSR along with drugs enlisted below.

Sl. No	Class of the Drugs	Name of the drugs	Countries adopted TSR
1	Antiretroviral Medicines[40]	Tenofovir[36] Zidovudine[41] Stavudine[41]	Kenya, Vietnam and Uganda[36] Zimbabwe[37] and South Africa countries[38]
2	Anti-TB Medicines	—	Zimbabwe[37] and South Africa countries[38]
3	Anti-Malarial Medicine	Artesunate plus sulfadoxine/pyrimethamine[39]	Mpumalanga[39]
3	Adverse Events Following Immunization(AEFI)	—	South Africa countries[38]

Table 3: Cohort Event Monitoring: Various countries conducted studies on CEM along with drugs enlisted below.

Sl. No	Class of the Drugs	Name of the drugs	Countries adopted CEM
1	Antiretroviral Medicines[51,54-56]		Belarus[53] Kwazulu-Natal,[54] Thailand,[55] Malawi[56]
2	Anti-TB Medicines	Bedaquiline,[43,46,57-59] Delamanid[43,46,60]	Philippines,[43] Armenia, Bangladesh, Belarus, North Korea, Ethiopia, Georgia, Indonesia, Kazakhstan, Kenya, Kyrgyzstan, Lesotho, Myanmar, Pakistan, Peru and South Africa,[46] India[57-60]
3	Anti-Malarial Medicine	artemisinin-based combination therapy,[42,45,53] Injectable Artesunate,[44]	Ghana,[42] Kenya,[42] Nigeria[42,45] and Zimbabwe[42] Uganda,[44] Tanzania[52,53]
3	Other Drugs	Quetiapine[47,48] Asenapine[47,49] Rivaroxaban[47,50]	

CONCLUSION

In India, the initiative was taken by PvPI in issuing the drug safety alerts generated through spontaneous reporting database, which gives a ray of hope in directing the research in pharmacovigilance towards the TSR and CEM, it may also ensure involving multi professional collaborations and more patient care faculty involvement in complete healthcare provision to the general public for considering the drug safety alerts as drug safety signals by national drug regulatory authority, i.e. Central Drugs Standard Control Organization in India.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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