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Pharmacovigilance: Practical Approaches to make it Serve its Purpose

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ABSTRACT: ***The Pharmacovigilance Programme of India (PvPI) was launched by Central Drug Standard Control Organization under the tutelage of Ministry of Health and Family Welfare, Government of India in July 2010. The main obstacle is under reporting which curbs the functioning of PvPI. AIMS AND OBJECTIVES: To identify practical approaches towards increasing effectiveness of PvPI in order to formulate a practicable rather than ideal on-paper plan. MATERIALS AND METHODS: After discussing various issues in regular clinical meets at our institute (NKPSIMS, Nagpur, M.S.) realistically implementable recommendations were taken into considerations without being overenthusiastic to contribute towards PvPI. Some of them were tested at our institute like compulsion for each undergraduate student to report at least two Adverse Drug Reactions (ADRs), lectures, Continued Medical Education (CME) and workshops on Pharmacovigilance. RESULTS: The results of these interventions were more than encouraging since we saw increased reporting, although results of some interventions were not quantitatively measurable. CONCLUSION: The present study has looked into several major aspects of the issue of underreporting of ADRs, and we suggest credible and practically executionable recommendations at each level of healthcare in order to increase reporting and help PvPI serve its purpose- to increase patient safety in terms of drug related problems. The present paper is a clamor for action by the medical fraternity and the regulatory establishments.***

KEYWORDS: Pharmacovigilance, interventions.

INTRODUCTION: Breakthrough in drug discovery has changed treatment plans vastly, although adverse drug reactions (ADRs) encountered with their use has also become common, most of which are avertible.[1,2] The after-effects of ADRs like increased duration of hospitalization, increased treatment expenses, increased morbidity and mortality consequently lead to increased burden on patients and health care system.[3] According to one study about 0.2% to about a quarter of all hospitalizations are due to ADRs and about 3.5 to 4% of them encounter grave ADRs. However major concern here is that above figures do not depict the actual amount of ADRs in community as these studies discount drug abuse and overdose related ADRs.[4] Pharmacovigilance (PV) as defined by World Health Organization (WHO) is a science and activities related to detection, assessment, understanding and prevention of adverse effects or any other drug-related problems.[5] It utilizes inputs from various sources like spontaneous reporting from health care professionals (HCPs), active surveillance, available literature, clinical trials, observational studies, periodic safety update reports of drug trials (PSURs) etc.[6] In India, amongst above mentioned sources of inputs, spontaneous reporting by any HCP including doctors, nurses and pharmacists, is most commonly relied upon.[7] It has many pros like it comprehends all known population and drugs, is economically feasible, easy going, and it identifies new risk groups while contributing additional information on known risk groups and ADRs.[8,9] ADRs from around the world are collected and maintained in electronic database by Uppsala monitoring centre (UMC) in collaboration with WHO with about 4.7 million case reports from 96 member countries. Still only 1/10th of total estimated ADRs are reported. The Pharmacovigilance Programme of India (PvPI) was launched by Central Drug Standard Control Organization under the tutelage of Ministry of Health and Family Welfare, Government of India in collaboration with Indian Pharmacopeia Commission (IPC) acting as National Co-ordination Centre (NCC) in July 2010. Due to deficient ADR reporting amongst HCPs, India although being the 2nd most populous country in the world has a bantam contribution towards UMC database.[10] PvPI although striving for indoctrinating favorable attitudes among HCPs (since HCPs are principal reporters) to report ADRs through relentless venture, underreporting is still existent on large scale[4,11,12,13,14,15] with underreporting rate of about 90%.[13] Such vast underreporting has deleterious effects in that it adjourns prompt recognition of ADR and consequently escalate morbidity and mortality.[16] Various factors have been identified for such underreporting through Knowledge, Attitude and Perceptions (KAP) studies.

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Inman has categorized these factors dramatically as "seven deadly sins" which include:

1. Legal attributes- fear of enquiry, aspiration to ADR data on personal fronts,
2. Financial incentives,
3. Diffidence/ uncertainty of diagnosis,
4. Complacency- thinking that serious ADRs are well documented till the time drug reaches market,
5. Indifference- belief that single ADR will not contribute to the cause,
6. Ignorance- belief that only serious ADR need to be reported,
7. Lethargy- deferment and impartiality in ADR reporting and other excuses.[17]

In order to increase participation of HCPs in PvPI it is mandatory that all HCPs are familiarized with process of ADR reporting.[18] Effective pharmacovigilance strategies will generate data which when made available at each level of healthcare will promote rational use of medicines, evidence based medicine and prevention of ADRs.[19,20] Keeping all this in mind the present study was undertaken to identify and try out various interventions that would lead to increased spontaneous reporting.

AIMS AND OBJECTIVES: The present study was conducted to fulfill following objectives:

1. Identify various interventions that would increase spontaneous reporting.
2. Identify various interventions that would increase awareness among HCPs to increase ADR reporting.
3. To test the efficacy of these interventions in increasing spontaneous ADR reporting.

MATERIALS AND METHODS: The present study was a non-randomized, prospective study carried out from January 2015 to June 2015 at NKP Salve Institute of Medical Sciences and Research Centre and Lata Mangeshkar Hospital, Nagpur (M.S.). The study was initiated after taking prior approval from Institutional Ethics Committee (IEC). The study participants were undergraduate (UGs) M.B.B.S students, postgraduate students (PGs). Before carrying out any intervention, it was necessary to evaluate the baseline KAP of the healthcare professionals regarding ADR monitoring and pharmacovigilance so that the intervention can be targeted, based on the specific findings. So, we took the findings of such study conducted at our institute in the current year [21] and other such study conducted elsewhere [10] to identify key areas of fallacies. The main factors identified in this studies were lack of knowledge on how to report, doubt of causality, belief that only serious side effects need to be reported, uncertainty over ADR diagnosis, belief that serious ADR are well documented by the time a drug is marketed, lack of time, non-availability of ADR reporting forms, fear of extra workload. Accordingly possible interventions were discussed in regular clinical meets at the institute to address the issue keeping one thing in mind- to formulate a practically implementable plan rather than ideal on-paper plan. Over the study period of 6 months interventions like mandatory 2 ADRs reporting by each UG student, 5 ADRs by each PG student, creation of "Whatsapp" group for addressing any queries on ADR reporting, making it mandatory for all institutional Randomized Control Trials (RCTs) to provide a detailed plan of ADR detection during the trial mentioned in Standard Operating Procedure (SOP) at the time of Institutional Ethics Committee (IEC) meeting for approval of RCT etc. (TABLE 1) Some of the interventions have been suggested to management team and will be implemented in due course of time. Basal number of ADR reports were noted for past one year prior to start of study and number of ADRs at end of the study were recorded to check the efficacy of interventions.

RESULTS: The present study included UGs of IInd year M.B.B.S, PGs of all clinical faculties. Basal/ pre-intervention ADR over past one year i.e. in 2014 was only 4 ADRs. During study period of 6 months total number of ADRs reported by UGs were 47, while PGs reported 16 ADR reports. Actual number of ADRs was 14 and the rest were repetitions. Other interventions were done to increase awareness, hence their impact on spontaneous ADR reporting was not measurable. At the end of study total number ADRs reported were counted to compare it with basal reporting rate in order to test efficacy. The results were

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encouraging as ADR reported during study period of 6 months were 14 compared to 4 ADRs in previous one year before the start of study.

DISCUSSION: From the finding of attitude related to ADR reporting at our institute in KAP study,[21] one important thing came to light that all Health Care Professionals (HCPs) encountered problem of "resistance to accept change" as the main culprit for underreporting. "Lewin's theory of change" to overcome such resistance was implemented into action, which takes into consideration the behavior of HCPs during the process of change and practical approaches to enhance behavior in favor of accepting the desired change.[22] This works in basic 3 steps:
Step 1- unfreezing the present state
Step 2- change to new/changed state
Step 3- refreezing at new/changed state.[23]
The present study is first of its kind, in India, to implement "Lewin's theory of change" in pursuit of transforming attitudes of HCPs to favorable level towards spontaneous ADR reporting. Currently we are at transition of step 1 and 2. All the interventions done in the present study (TABLE 1) act as positive force towards bringing the desired change in attitudes. However, just as evolution of man, process of change is also slow and therefore continuous perceptive and intellectual support is obligatory [24] and this can be achieved through consistently timed Continued Medical Education (CMEs), workshops, counselling, lectures and dedicated helpline number (televigilance) to address any ADR reporting related queries. In the present study we made 2 and 5 ADRs reporting mandatory for UG and PG student respectively. This intervention had an added advantage that it goes well with attitudes of UGs in that UGs are exposed to patient care for the first time in their career, so they are more interested to contribute towards patient safety. It is basic human nature that any good deed needs to be appreciated and based on this notion we tried giving feedback to ADR reporters as soon as they reported an ADR. Feedback was given through text messages on mobile phones in the form of encouraging and appreciable dialogue like "thanks for reporting, your single ADR report will help in reducing morbidity and mortality of number of patients" in pursuit of encouraging them to continue reporting ADRs. "Lack of time" was reported consistently in many KAP studies as factor for underreporting.[10,21] To overcome this hurdle we tried creating whatsapp group (in view of present tech savvy generation of HCPs). We also divided all clinical wards amongst all teaching staff and PGs of Pharmacology department who would visit their respective wards on a daily basis in order to notify ADRs, if any. The only thing needed was to report about ADR on whatsapp or through televigilance and concerned pharmacologist would reach at the ward to assist in ADR reporting. This maneuvers changed attitudes of HCPs towards favorable one, since it saved time and we eased all the procedures of reporting by continuous support, thus creating an ultimate attitude that reporting ADR does not consume time and there is no extra workload in doing so. Relation between HCPs also plays a vital role in shaping attitudes towards ADR reporting. To increase awareness we made lectures, CMEs on PV compulsory for UGs and PGs, since this stage is the molding stage in career of HCPs. The main theme of these interventions was to increase reporting of adverse events, so that ADRs due to drug-drug interactions, ADRs with no palpable cause are also caught in the trap. Also to increase spontaneous reporting by the patient we organized plays in hospital premises conveying the message of importance of ADR reporting in addition to how and where to report. This is in conjunction with document released by WHO titled "Safety monitoring of medicinal products-Reporting system for the general public" which states that problem of underreporting can be minimized significantly through amalgamation of extra source of ADR related data with spontaneous report by the patient. The chances of bias are also reduced, since patient is unaware of medical knowledge of ADR.[25] Also, from the findings of one study, it is safe to conclude that newfangled ADRs can be spotted rapidly through patient reporting.[26] These plays were organized keeping in mind basic mentality of local population. Providing a separate section of suspected ADR in patient record sheet is also in the pipeline, since while writing daily notes HCP will note

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down the ADR, if any, without forget. This will be reported directly by HCP or by Pharmacologist on daily visit to his/her allotted clinical ward.

In addition, certain recommendations at level of each stakeholder were proposed, to increase spontaneous reporting which were practically feasible to implement. These included making inspection of PV in medical colleges compulsory during Medical Council of India (MCI) inspection, mandatory workshop of 3 days for PGs just as research methodology by state medical committee, mandatory PV centre for all private and corporate hospitals during inspection by hospital accreditation agencies like NABH, compulsory questions on PV in UG, PG and PG entrance exams by state heath educations regulatory bodies and MCI, introduction of PG diploma course in PV by MCI, use of media like newspapers, television, Frequency Modulation (FM) radio, collaboration of PvPI with other national disease control programmes like Revised National Tuberculosis Control Programme (RNTCP) by Ministry of Family and Health Welfare. Also immediate feedback to ADR reporters on national scale and setting up of Adverse event Following Immunization (AEFI) monitoring team mandatory for all PvPI centres by PvPI, making PSURs monthly for 1 year in case drugs for acute conditions and 3 monthly for 5 years in post marketing phase instead of currently practiced 6 monthly reporting for first 2 years thereafter annually for 2 years mandatory by DCGI, decentralization of patient reporting process due to wide disparities in language and ethos by NCC. With the advent of newer drugs and resulting increase in arsenal of available medicines, the horizons of PV are also consistently expanding not limiting to just monitoring of ADRs. It is diligently related to problems arising from drug abuse, drug-drug interactions, polypharmacy, use of illegal drugs and over the counter drugs. Therefore, while formulating strategies it is indispensable to keep in mind that these strategies should cover all above mentioned aspects and also include ADRs due to vaccines, blood products, herbal medicines, etc.[27] Therefore we have suggested on constructing a separate team for monitoring of vaccine/s related ADRs in front of management team of our institute. Erice declaration should be implemented at international levels, which states that sharing of ADR related data must be invigorated between countries in view of increasing patient safety.[28] Finally, generic market is largest supplier of essential drugs in the country. Therefore they need to be subjected to stringent safety monitoring processes, since essential drugs are used by majority of the population.

CONCLUSION: Active involvement and reinforcement of HCPs in the PvPI is need of the hour to avoid morbidity, mortality and economic burden owing to prolonged hospitalization due to ADRs. Also the involvement of nursing staff should be fortified since they are continuously in close vicinity of the patient. The practical approaches to increase spontaneous reporting mentioned in the present study should be implemented and tested for efficacy across whole country so that generalized findings will be available in front of regulatory authorities and other policy makers, before planning any new strategies on PV, thus helping it serve its purpose- to increase patient safety.

REFERENCES:

1. McDonnell PJ, Jacobs MR. Hospital admissions resulting from preventable adverse drug reactions. Ann Pharmacother. 2002;36:1331–6. [PubMed]
2. Bates DW, Cullen DJ, Laird N, Peterson LA, Small SD, Servi D, et al. Incidence of adverse drug events and potential adverse drug events. Implications for prevention. J Am Med Assoc. 1995;274:29–34. [PubMed]
3. Wasserfallen JB, Livio F, Buclin T, Tillet L, Yersin B, Biollaz J. Rate, type and cost of adverse drug reactions in emergency department admissions. Eur J Intern Med. 2001;12:442–7. [PubMed]
4. Rehan HS, Vasudev K, Tripathi CD. Adverse drug reaction monitoring: knowledge, attitude and practices of medical students and prescribers. Natl Med J India. 2002;15(1):24-6.

ISSN: 2519-9889

5. S.Africa Draft Guidelines, 2007. Available from http://www.epnetwork.org/Resources/Pharmacovigilance/WHO-draft-guidelines-pharmacovigilance.pdf. Accessed on 2 June 2015.
6. Guidelines on Good Pharmacovigilance practices (GVP) Module IX-Signal management, 2012. Available from http:// www.ema.europa.ea/docs/en_GB/document library/Scientific_guideline/2012/06/WC500129138.pdf. Accessed on 21 June 2012.
7. Upadhyaya P, Seth V, Moghe VV, Sharma M, Ahmed M. Knowledge of adverse drug reaction reporting in first year postgraduate doctors in a medical college. Ther Clin Risk Manage. 2012;8:307–12. [PMC free article] [PubMed]
8. Desai CK, Iyer G, Panchal J, Shah S, Dikshit RK. An evaluation of knowledge, attitude and practice of adverse drug reaction reporting among prescribers at a teriary care hospital. Perspect Clin Res. 2011;2(4):129-136.
9. Guidance for Industry: Pharmacovigilance Requirement for Biological Products, 2014. Available from http://cdsco.nic.in/writereaddata/Pharmacovigilance_guidance_Final2014.doc.
10. Gupta P, Udupa A. Adverse drug reaction reporting and pharmacovigilance: knowledge, attitudes and perceptions among resident doctors. J Pharm Sci & Res. 2011;3(2):1064-69.
11. Khan SA, Goyal C, Chandel N, Rafi M. Knowledge, attitude and practice of doctors to adverse drug reaction reporting in a teaching hospital in India: An observational study. J Nat Sci Biol Med. 2013;4:191–6. [PMC free article] [PubMed]
12. Williams D, Feely J. Underreporting of adverse drug reactions: attitudes of Irish doctors. Ir J Med Sci. 1999; 168:257-261.
13. Hazell L, Shakir SA. Under-reporting of adverse drug 14. reactions: a systemic review. *Drug Saf* 2006; *29* : 385-96.
14. Kalaiselvan V, Prakash J, Singh GN. Pharmacovigilance 15. Programme of India. *Arc Pharmacy Pract* 2012; *3* : 229-32.
15. Bates DW, Cullen DJ, Laird N, Petersen LA, Small SD, et al. (1995) Incidence of adverse drug events and potential adverse drug events. Implications for prevention. ADE Prevention Study Group. JAMA 274:29-34.
16. John LJ, Mohamad A. Reporting of ADR: an exploratory study among nurses in a technical hospital. Ajman, United Arab Emirates. Daru J Pharm Sci. 2012;20(44):2-6.
17. Inman WH. Attitudes to adverse drug-reaction reporting. Br J Clin Pharmacol. 1996;41:433–5. [PubMed]
18. Rehan HS, Chopra D, Sah RK, Mishra R. Adverse drug reactions: Trends in a tertiary care hospital. Curr Drug Saf. 2012;7:384–8. [PubMed]
19. Pirmohamed M, James S, Meakin S, Green C, Scott AK, et al. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18820 patients. Br Med J 2004, 329:15-19.
20. Martinez-Mir I, Garcia-Lopez M, Palop V, Ferrer JM, Rubio E, Morales- Olivas FJ: A prospective study of adverse drug reactions in hospitalized children. Br J Clin Pharmacol 1999, 47:681-688.
21. Dharmadhikari PP, Date AP, Patil KS. Knowledge, attitude and practice among healthcare professionals of adverse drug reactions reporting in a tertiary care centre. Int J Basic Clin Pharmacol 2015;4:300-5.
22. Bozak MG (2003) Using Lewin's force field analysis in implementing a nursing information system. Comput Inform Nurs 21: 80-85.
23. Lewin K, Cartwright D. Field theory in social science: Selected theoretical papers. 1951,Harper & Brothers, New York.
24. Holbeche L. Understanding change. In editor: Linda Holbeche. Theory, Implementation and Success,2007 4th ed Oxford: Elsevier.

ISSN: 2519-9889

25. Safety Monitoring of Medicinal Products: Reporting System for General Public, 2012. Available from http://www.who.int/medicines/areas/quality_safety/safety_efficacy/EMP_ConsumerReporting_web_v2.pdf. Accessed on 3rd April 2015.
26. Serotonin re-uptake inhibitors (SRIs) and shock-like paraesthesia. Lareb documents,2002 http://www.lareb.nl/LarebCorporateWebsite/media/publicaties/kwb_2002_2_ssris.pdf. Accessed on 15 Dec 2011.
27. The Importance of Pharmacovigilance: Safety Monitoring of Medicinal Products, 2002. Available from http://apps.who.int/medicinedocs/pdf/s4893e/s4893e.pdf. Accessed on 4th April 2015.
28. The Safety of Medicines in Public Health Programmes: Pharmacovigilance an Essential Tool, 2006. Available from http://www.who.int/medicines/areas/quality_safety/safety_efficacy?Pharmacovigilance_B.pdf. Accessed on 20th April 2006.

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TABLE 1: EFFECT OF INTERVENTIONS ON ADR REPORTING RATE

Intervention
1. Compulsory 2 ADRs/UG student
2. Compulsory 5 ADRs/PG student
3. Feedback to ADR reporters
4. Mandatory for all RCTs to give detailed ADR detection plan in SOP by IEC prior to approval
5. Creation of whatsapp group for ADR reporting
6. Division of wards to each teaching staff and PGs of Pharmacology
7. Availability of ADR reporting forms in all wards 24x7
8. Mandatory lectures on PV for UGs
9. Mandatory PG activity on PV in all MD/MS courses
10. Conducting CME/Workshop on PV
11. Setting up of dedicated telephone extension for ADR reporting/Televigilance
12. Sample of duly filled ADR reporting form in each ward and in mobile of each HCP
13. Appealing "plays" on importance of ADR reporting in hospital premises
14. Separate section of S/E on patient/case record sheet
15. Printed booklets regarding possible ADRs and DDIs and their drugs in each ward
16. Mandatory 5 MCQs on PV from 2nd to 4th year UG
17. Setting up of separate team for vaccine related ADR
18. Designing and dispatching of patient ADR reporting form in local language

Note:
1 to 7- interventions which were targeted to directly impact on spontaneous ADR reporting
8 to 13- interventions done to increase awareness regarding ADR reporting
14 to 18- interventions suggested to management team

