

Impact of periodic safety update reporting system: A preliminary trial in a tertiary care teaching hospital of southern India

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ABSTRACT

The objective of this study was to assess the impact of implemented periodic safety update report (PSUR) system in our hospital via PSUR function assessment questionnaire (PFAQ) vetted by Delphi panel and by comparing frequency and rate of adverse drug reaction (ADR) reporting for three highly prescribed drugs. An PFAQ was validated by Delphi panel, in two successive rounds of revision and used to record the responses on Likert scale. Drugs with well-known ADR profiles in published literature were considered reliable markers of the impact of PSUR system implementation. Pre-PSUR retrospective data retrieved from medical records for 9 months and compared with the trend of frequency and rate of ADR reporting post-PSUR system implementation. Frequency and rate of ADR reporting for selected drugs rose by 68% post-PSUR system implementation. Participation of wards in ADR reporting and reporting of unexpected/unreported ADRs was also seen increased. Numbers of PFAQ responses for each performance indicator corresponding to the respective success factors were seen shifting favorably on the Likert scale in phase 2 study period. This study illustrates how drug safety reporting network can be established by reallocating existing resources, with minimal expenses on training/human resources and to improve poorly designed pharmacovigilance system in India that relies heavily on data from overseas.

INTRODUCTION

The World Health Organization (WHO) defines pharmacovigilance (PV) as “the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects of drugs. An adverse drug reaction (ADR) is a reaction to a drug and/or a combination of drugs which is harmful and unintended and which occurs at a dose that is normally used for prophylaxis, diagnosis, or treatment” (Aronson, 2012; Coulter, 2013). In 2013, India's share in globally reported ADRs was only 2%. ADRs reported per million almost doubled in the last few years to 40 but remains far less than in developed nations. Indian regulatory bodies

assess the benefit–risk ratio of drugs based entirely on the experience gathered overseas; it has become both urgent and important for India to develop indigenous PV systems. The accumulating evidence suggests that reporting suspected ADRs adds value to PV through the generation of potential signals, and describing potential ADRs in sufficient detail to assess likely causality and reduce the impact of ADRs (Alvarez *et al.*, 2010).

The ADRs entail the unjustified hospital admissions, worsen the hazards from the prevailing shortage of trained health professionals, increase the preventable health hazards, diminish the quality of life, and waste both resources and money. International data revealed that 4.1% of the non-elderly hospital admissions were ADR-related, while it was four times higher for elderly (16.6%) (Beijer and De Blaeys, 2002).

A study carried out in south India demonstrated that 0.7% of hospital admissions were due to ADRs, with a total of

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3.7% of hospitalized patients experiencing at least one ADR, of which 1.3% were fatal (Ramesh and Parthasarathi, 2009). Another study in India showed that ADRs accounted for 3.4% of the hospital admissions while 3.7% patients developed ADRs during their hospital stay (Arulmani *et al.*, 2008). Yet, another study in Europe showed that 41.2% (42 out of 102) ADRs were preventable if clinical safety surveillance programs were implemented (Dormann *et al.*, 2003).

As newer safety data emerge, safeguarding public health is vital before withdrawing a drug or altering its labeling. Improving the ADR reporting would lead to improved indigenous databases from which we may draw locally relevant safety guidelines. Methods for improving the reporting of ADRs include: (1) early initiation and enforcement of risk management plans by the regulator, (2) education of all those eligible to report, (3) greater transparency of regulatory decisions, and (4) better and quicker dissemination of updates in safety information (Tang, 2010).

The PV and safety monitoring, being barely a decade old in India, are a relatively new concept in this country. On the other hand, the ever-rising number of global clinical trials being conducted in India, along with the increasing number of new drug approvals with the limited drug safety data, together underscores the need for a robust PV system that is in line with international norms (Brahmachari *et al.*, 2011).

Periodic safety update report (PSUR) is defined as “an update of the worldwide safety experience of a medicinal product submitted to competent authorities at defined times post-authorization. According to regulatory norms, the marketing authorization holders (MAHs) must prepare PSURs and make them available to the regulatory authority” (Amy Tang, 2010).

It is important to note that all major drugs were being sold in the Indian market at the time of withdrawal. Indian regulatory bodies have been relying on the experience gathered overseas to assess the benefit–risk ratio of a drug, making it imperative for India to develop its own PV system. High profile drug withdrawals that drew the attention of Drugs Controller General of India (DCGI) and WHO alike, highlighted the inadequacy of PV systems implemented by MAHs in India (Arora, 2012).

Schedule Y of Drug and Cosmetics Act 1945 stipulates legislative requirements for PV in India. Following multiple incidents of high-profile drug withdrawals, Schedule Y was thoroughly reviewed and amended in January 2005 to ensure adequate PV compliance by the MAHs. Schedule Y contains a section on post-marketing surveillance with guidelines and requirements for PSUR cycle, a template for PSUR, PSUR submissions, and the timelines for expedited reporting. The revised Schedule Y recommends that “for all new products, PSURs should be submitted every 6 months for the first 2 years and thereafter annually for the next 2 years”. Schedule Y has adopted the same format of PSUR as given in ICH E2C (Arora, 2012).

A previous study noted that PSUR evaluations contributed to 38% of post-authorization regulatory actions in a sample of bio-pharmaceuticals (Ebberts *et al.*, 2012). In addition, in 2010, another study observed that 64% of a selection of ADRs originated from PSURs (Alvarez *et al.*, 2010).

Reports of myocardial infarctions and strokes in patients taking Vioxx® resulted in its withdrawal from the market in 2004.

Likewise, Lipobay® (Baycol®; cerivastatin), a hypolipidemic drug; fenfluramine and dexfenfluramine, an anti-obesity drug in addition to many others, were voluntarily withdrawn by MAHs due to safety reasons. Experts have suggested that only a probationary license should be given for a new drug, which should be confirmed only when drug post-marketing studies demonstrate acceptable risk–benefit balance (Greener, 2005). The latest data from the website of central drug standard control organization (CDSCO), the Indian drug regulatory authority, indicate that around 90 drugs or their combinations were withdrawn from the market because of their low-safety profile (CDSCO, 2009).

Though rules in India mandate that after launching a drug, its side-effects, fatalities, and injuries in Indian patients need to be documented, MAHs often do not comply with the guidelines (Sinha, 2012). When the Indian government constituted a parliamentary standing committee to scrutinize the compliance of PSUR submissions, the CDSCO could supply only eight reports from a randomly selected 42 newly introduced drugs. The standing committee report says: “The committee takes strong exception to such rampant violation of the mandatory requirements. The committee recommends that the Union Health Ministry should direct the CDSCO to send a stern warning to all manufacturers of new drugs to comply with PSURs or face suspension of marketing approval. The committee is of the firm view that there is a poor follow-up of side-effects in Indian patients both by doctors and MAHs” (Indian parliamentary standing committee report, 2013).

After the parliamentary standing committee reported on the issue, CDSCO, in August 2012, amended the guidelines for mandatory submission of PSURs for all the MAHs within the given timeline. The CDSCO also issued orders to a few major hospitals in the country to submit PSURs for all drugs launched since 2011 and are being prescribed in the respective hospitals (CDSCO, 2013).

The Delphi method is a useful way of discovering and determining uncertainties and has been widely exploited in medical and health services (Akins, 2005). The Delphi method is a collaborative expert system where the experts are provided with a Delphi design and where they dynamically and actively contribute their knowledge to the system. This method significantly broadens the knowledge and effective decision making in health and social care (Hasson *et al.*, 2000; Shariff, 2015).

To measure opinions, perceptions, and behaviors, Likert scales are the most preferred among others. This method let us reveal the degree of outlook that possibly constructs a real difference in understanding the feedback. It can also give a better understanding of areas where you need to focus more and improve the process and function. Compared to binary questions, which give you only two answer options, it can help decide whether you strongly agree or strongly disagree with any system or process (Survey monkey, 2018).

In this context, we decided to design a system for implementing the PSUR reporting system in all wards of our hospital in accordance with the regulatory requirement. We also evaluated the quality of functioning of PSUR system implemented in our hospital with the help of a PSUR function assessment questionnaire (PFAQ), which was subsequently validated by a Delphi panel, before it was circulated among the healthcare practitioners (HCPs). Test samples of three highly prescribed

drugs, with already known ADRs, were chosen to evaluate the functioning of PSUR system. On the other hand, the impact of PSUR system implementation was evaluated by comparing the frequency and rate of ADR reporting for selected three drugs before and after the implementation of PSUR system.

MATERIALS AND METHODS

Implementation of PSUR system in the hospital

Ethical permission was obtained from the institutional ethics committee of the hospital before starting the study (Ref: IEC 195/2013). A PSUR committee was formed in January 2013 to carry out ADR documenting, preparation, and submission of PSURs. Drug information leaflets, ADR reporting guidelines, and ADR reporting forms were prepared and circulated in all wards of a hospital for manual ADR reporting. ADR reporting software was also developed and linked with the intranet website of the hospital for online reporting of ADRs. Appropriate training on the basics of ADR, manual and online ADR reporting for newer drugs under PSUR system was provided to HCPs. Hands-on training on a medical dictionary for regulatory activities (MedDRA) coding software, Vigiflow and hospital information services software (hospitals internal patient management and billing software) were provided to Pharm D interns and students.

Evaluation of the impact of PSUR system implementation using validated PFAQ

The quality of system implementation was evaluated using a duly validated questionnaire vetted by a Delphi panel of 10 members consisting of in-house clinical pharmacist, chief nurse/pharmacist, physician, and faculty members from Department of Pharmacy Practice. Success factors and performance indicators listed in PFAQ were successively added or deleted by the Delphi panel, in two successive rounds of revision, yielding the final draft of PFAQ. Final PFAQ draft lists 11 success factors and 8 performance indicators based on which 88 questions were listed in the final PFAQ form. The sample size for two proportions (responses on PFAQ for the particular time, phase 1 and phase 2) was calculated to 40 respondents in each phase considering 500 HCPs population size in a hospital with a confidence interval of 95% and margin of error 15%. Final PFAQ was circulated among

HCPs (physicians, nurses, pharmacists, interns, and Pharm D students) to rate their responses on the Likert scale of 1–5 where 1 corresponds to “very good” and 5 corresponds to “very poor.”

Evaluation of the impact of PSUR system implementation and functioning using safety surveillance of three highly prescribed drugs

On account of paucity of data, it was not possible to judge the quality and extent of ADR reporting of newer drugs. Therefore, changes in the pattern, frequency, and rate of ADR reporting for three widely prescribed drugs, namely, amlodipine, furosemide, and risperidone were taken as a proxy to the impact of PSUR system implementation. It was necessary to choose drugs with well-known ADR profiles in published literature to be considered reliable markers of the impact of PSUR system implementation. The study period lasted 18 months, divided into two intervals, namely 9 months before and 9 months after PSUR system implementation. The ADR data were collected from the medical records retrospectively for the first 9 months before the PSUR system was implemented. After the HCPs (physicians, nurses, pharmacists, interns, and Pharm D students) were trained and familiarized with the system of PSUR, the ADR data for the above drugs were again captured and compared with the 9 months post-PSUR system implementation. The differences in ADRs were captured in terms of number, category, frequency, rates, and locations where ADRs were encountered.

RESULTS

Evaluation of the impact of PSUR system implementation using validated PFAQ

The preliminary draft PFAQ contained 19 items (10 success factors and 09 performance indicators) for evaluation and it was sent out to all 10 panel members in round 1 of the Delphi process. The first review round of PFAQ (Table 1) item validation was initiated on July 1, 2014. The responses on PFAQ from all the panel members were completed and received on August 20, 2014. All 19 items mentioned in PFAQ draft were answered and received in the first review round. Expert panel members reached 70% consensus to include (aggregate percentage of Likert scales 1 and 2) seven success factors and eight performance indicators in

Table 1. Preliminary list of success factor's and performance indicator's circulated in first review round of PFAQ validation.

S. No.	Success factors	Likert scale					Performance indicators	Likert scale				
		1	2	3	4	5		1	2	3	4	5
1	Latest drug list						Information					
2	Drug brands						Awareness					
3	Reporting of IP nos.						Accessibility					
4	Patient follow-up						Relevance					
5	Collection of ADRs						Training					
6	Reporting of ADRs						Practicability					
7	Safety review						Communication					
8	Periodic review and analysis						Quantity of data					
9	Preparation of PSUR						Quality of data					
10	Submission of PSUR											
	Average rating											

Likert scale: 1, strongly agree; 2, agree; 3, neutral; 4, disagree; 5, strongly disagree.

Table 2. Updated list of success factor's and performance indicator's circulated in second review round of PFAQ validation.

S. No.	Success factors	Likert scale					Performance indicators	Likert scale				
		1	2	3	4	5		1	2	3	4	5
1	Drug dispensing database						Information					
2	Drug brands						Awareness					
3	Wards/departments						Accessibility					
4	Nursing station						Relevance					
5	Pharmacy						Training					
6	Collection of ADRs						communication					
7	Reporting of ADRs						Quantity of data					
8	Safety review						Quality of data					
9	Periodic review and analysis						Overall feed back					
10	Preparation of PSUR											
11	Submission of PSUR											
	Average rating											

Likert scale: 1, strongly agree; 2, agree; 3, neutral; 4, disagree; 5, strongly disagree.

PFAQ. However, panel also reached to 70% consensus to exclude (aggregate percentage of Likert scale 4 and 5) three success factors (latest drug list, reporting of IP numbers, and patient follow-up) and one performance indicator, practicability. Delphi panel also suggested considering some additional success factors (drug dispensing database, wards/departments, nursing station, and pharmacy) and performance indicator (overall feedback) to be included in the second review round of PFAQ. The updated list of 20 items (success factors and performance indicators) based on first review responses for PFAQ was circulated for second review round to Delphi expert panel on September 1, 2014 (Table 2). Delphi panel provided responses to all the PFAQ items on October 31, 2014. In the second review round, 70% consensus was achieved for seven success factors to include them in final PFAQ and to exclude three success factors (drug brands, safety review, and periodic review and analysis) and one performance indicator (relevance). Additionally, there have been strong proposal by Delphi panel to include four more success factors (safety review/consultation, review and analysis of data, ADR data, and PSUR news-letter) in the final PFAQ.

Total 88 questions were framed and included in final PFAQ based on the validated success factors and performance indicators vetted by Delphi panel during first and final review rounds. The consensus was considered reached if at least 70% of the expert panel members strongly agree or disagree that success factors and performance indicators should be included or excluded in the final PFAQ. The questions were framed for each 11 success factors to assess their success for implemented PSUR system using eight validated performance indicators (11 success factors \times 8 performance indicators = 88 questions) shown in Table 3. Responses to each question were recorded on a Likert scale of 1–5 where 1 corresponds to very good and 5 corresponds to very poor. The structure of PFAQ with the examples of few questions included in PFAQ are given below in Table 4.

One hundred sixty PFAQs were circulated in the different wards of hospitals from November 15, 2014 until May 16, 2016. Total 94 filled PFAQs responses were received until May 16, 2016. The PFAQ responses were recorded in two phases of 9 months interval each. The PFAQs received in the first 9 months were kept

in phase 1 (November 15, 2014 to August 15, 2015) and remaining PFAQs received in last 9 months were kept in phase 2 (August 16, 2015 to May 16, 2016). There were 46 responses received in phase 1 and 48 responses in phase 2 from HCPs.

Responses on success factor, overall assessment of the functioning of PSUR system reflect the success of PSUR implementation which indicates there is a significant improvement in the performance indicators rated by HCPs during the phase 2 study period compared with phase 1 study phase. Feedback by HCPs on overall assessment seen shifted favorably in phase 2 study period (68.7%) on the Likert scale 1 (very good) and 2 (good) compared with phase 1 (50%) as shown in Figure 1.

Evaluation of the impact of PSUR system implementation and functioning using safety surveillance of three highly prescribed drugs

The results presented here have been compiled from the data spread across 18 months (March 2013 to August 2014) both before and after implementation of PSUR system. In these 18 months, a total of 2,827 patients were prescribed amlodipine, furosemide, or risperidone in the hospital. ADRs reported for the above three drugs rose from 65 in the first 9 months (pre-PSUR) to 107 during the subsequent 9 months (post-PSUR). Overall, there was a 68% rise in ADR reporting rate from the different wards of hospitals for selected three drugs after the implementation of PSUR system.

Of the reported 172 ADRs for the 18 months study period, 30 ADRs were reported from amlodipine, 102 ADRs from furosemide, and 40 ADRs were reported from risperidone. All these reported ADRs for study duration were assessed for their severity using Hartwig severity scale. Thompson and Rawlins ADR classifications method was used to assess types of ADRs. Naranjo scale was used to assess causality of ADRs. Seriousness, outcome, and length of hospitalization increased due to ADRs were also assessed as shown in Table 5. Overall, there were 8.1% ADRs were found to be severe in nature, while 55.2% ADRs were analyzed as mild in severity. Severity of reported ADRs was found to be on higher side prior to PSUR system implementation (severe 5.1%; moderate 26%). Seven (7) out of 172 ADRs were

Table 3. Validated success factors and performance indicators by Delphi panel included in final PFAQ.

S. No.	Performance indicators	Drug information					Accessibility					Awareness					Training					Communication					Quantity of data					Quality of data					Overall feedback																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																										
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Likert scale: 1, very good; 2, good; 3, average; 4, poor; 5, very poor.

categorized to Type B reactions (idiosyncratic). Of the seven reported type B ADRs, four ADRs were reported prior PSUR system implementation. Totally, 11 (6.39%) patients were reported to have life threatening conditions of which five patients were reported to have life threatening conditions prior to PSUR system implementation. Increased in length of hospitalizations due to ADRs were experienced by 32 (18.6%) patients of which 10% patients have been identified post-PSUR implementation. There were 14 ADRs assessed to have probable associations between the event and study drug; most of these ADRs (6%) were reported post-PSUR system implementation. The outcome of 11 ADRs (6 ADRs reported prior PSUR implementation) were reported as fatal while 15 ADRs (all ADRs reported post PSUR implementation) were still continuing while the ADRs have been recorded. The average increase in hospitalization due to ADRs was recorded to be 3 days.

Implementation of PSUR system raised the ADR reporting rates for amlodipine (from 2% to 4.62%), furosemide (5.69% to 9%), and risperidone (from 6.12% to 10%). The overall rate of ADR reporting rose from 4.60% to 7.87% post-PSUR system implementation (Tables 6 and Fig. 2).

The frequency of ADR reporting increased manifold post-PSUR system implementation. For instance, reports of pedal oedema in amlodipine users increased from 40% to 70% after PSUR implementation (Fig. 3). Although ADRs for amlodipine were reported from many wards like psychiatry, medicine, and cardiology; the maximum increase (75%) came from medicine ward (Fig. 4).

Similarly, there was a significant rise in reports of hyponatremia (28.5% to 45.1%) and hypokalemia (27.5% to 50%) with furosemide post-PSUR system implementation (Fig. 5). This is possibly because of increased awareness and alertness about this clinically significant category. ADR reporting on furosemide from nephrology and cardiology wards increased significantly from 5% to 37% and 25% to 29%, respectively (Fig. 6).

Likewise, ADR reports for risperidone from psychiatry ward increased from 6.12% to 10% post-PSUR system implementation. Of these, nine ADRs were never reported before PSUR were implemented. Reports of extrapyramidal symptoms and tremors rose from 13.3% to 16% and 33.3% to 36%, respectively, post-PSUR, indicating greater awareness of important complications of therapy (Fig. 7).

DISCUSSIONS

This is among the first studies conducted in a health care setting in India to assess the process, functioning, and implementation of drug safety reporting network in a tertiary care hospital. Therefore, there is a lack of data available from similar studies to compare the outcomes of this study. We have discussed here the outcomes along with indicators of the selection process carried out via Delphi methods and perception of HCPs toward ADR reporting, which have been reported in other developed countries.

There are not any specific guidelines suggesting what should be the ideal Delphi panel size require carrying out Delphi survey because panel size is purposely selected and it depends on the problem being investigated. Delphi survey studies do not represent the panel size to be used in terms of statistical purposes; therefore, sample size determination for Delphi

Table 4. Structure of final PFAQ based on validated success factors and performance indicators.

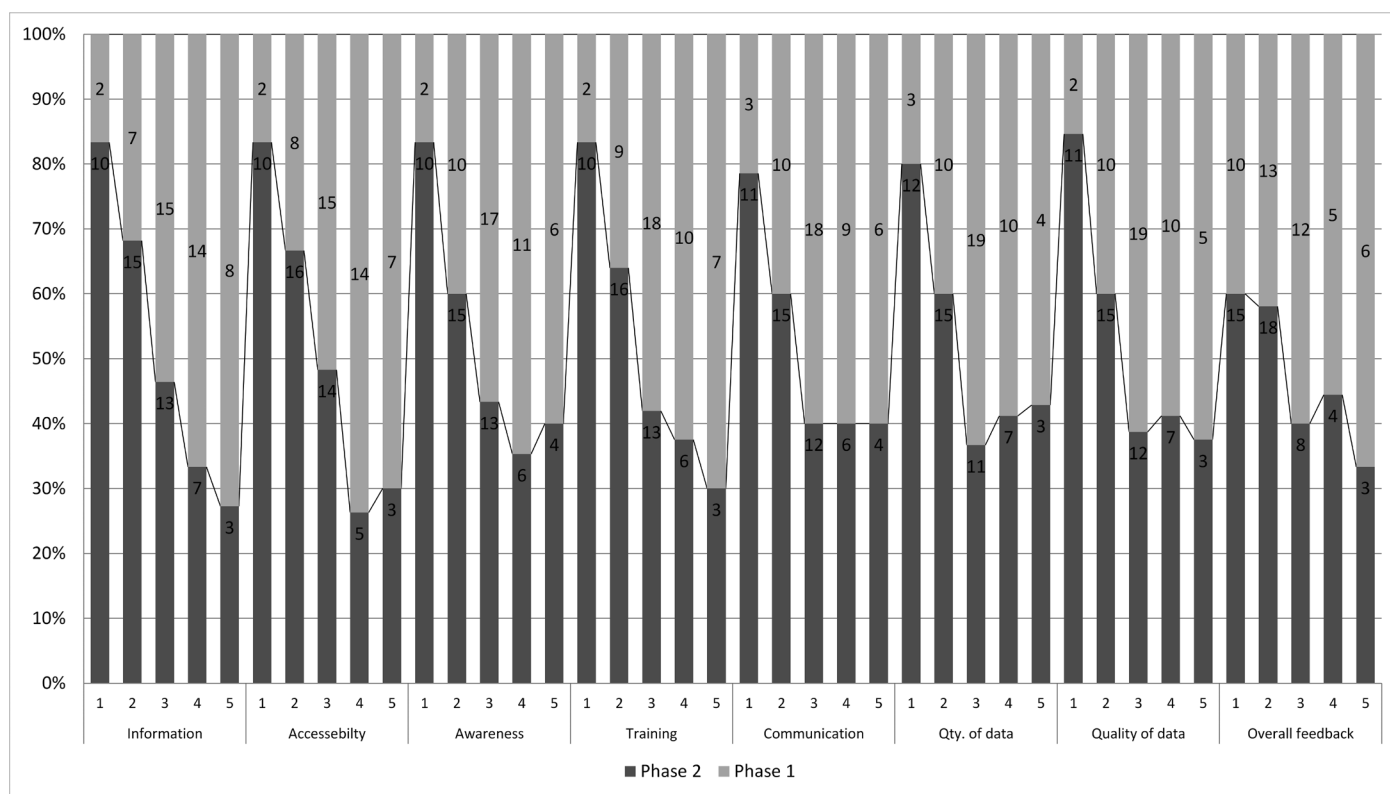
Success factors	Performance indicators	Questions in final PFAQ
		Responses recorded on Likert scale*
PSUR work station	Drug Information	Drug information available for the drugs included under PSUR?
Drug dispensing database	Accessibility	Access to drug details available in online drug dispensing database?
Wards/departments	Awareness	Awareness about the drugs given under PSUR and process of ADR reporting?
Nursing station	Training	The Benefits of training provided for ADR reporting under PSUR, if any?
Pharmacy	Communication	Communications with PSUR work station on any query related to ADR reporting?
Reporting of ADRs	Quantity of data	Satisfaction with the quantity of data reported under PSUR?
Collection of ADRs	Quality of data	Satisfaction with the quality of data collected for reporting under PSUR?
Safety review/consultation	Overall Feedback	Overall feedback on safety review and consultation under PSUR?
ADR data	Accessibility	ADR Information available for the drugs included under PSUR?
Review & analysis of data	Communication	Communications with the PSUR team on how to retrieve and see review and analysis reports for the reported ADRs under PSUR?
PSUR preparation	Training	Benefits of training on PSUR report preparations, if any?
PSUR submission	Quality of data	Quality of the data included PSUR?
PSUR news-letter	Accessibility	Accessibility of the PSUR news-letters?

*Likert scale: 1, very good; 2, good; 3, average; 4, poor; 5, very poor.

panel has completely different approach than other surveys (Shariff, 2015). Thus, we selected optimum panel size of 10 members to be involved in two review rounds of success factors and performance indicators validation and PFAQ finalization.

Likert scale was used in this study to validate performance indicators and success factors and finalize the PFAQ via Delphi panel. Also, it was requested from HCPs to rate their

responses on the Likert scale in PFAQ on implemented drug safety network and PSUR system in the hospital. We have observed the responses received on Likert five-point rating scales gives more power to concerned query compared with binary questions, which only gives two answer options. Likert scale helps to decide HCPs whether they are strongly agree or strongly disagree with any system or process (Alshakka *et al.*, 2013; Survey Monkey, 2018).



Likert scale (values 1: Very good; 2: Good; 3: Average; 4: Poor; 5: Very poor)

Fig 1. Overall assessment of Implemented PSUR system in different wards of hospital via PFAQ responses received during the phase 1 and phase 2 study duration.

Table 5. Assessment of ADRs for their severity, type, seriousness, causality, length of hospitalization and outcome.

Drug	Severity			Type		Seriousness		Causality			Outcome			Hospitalization prolonged*
	Mild	Moderate	Severe	Type A	Type B	Hospitalization prolonged [#]	Life threatening	Probable	Possible	Recovering	Recovered	Continuing	Fatal	
Amlodipine	15	10	5	28	2	7	2	3	27	10	11	7	2	3.5
Furosemide	60	38	4	99	3	15	6	9	93	32	60	4	6	2.5
Risperidone	20	15	5	38	2	10	3	2	38	5	28	4	3	3.0
Total	95	63	14	165	7	32	11	14	158	47	99	15	11	3*
%	55.2%	36.6%	8.1%	96%	4%	18.6%	6.39%	8.1%	91.8%	27.3%	57.5%	8.7%	6.3%	--

[‡]Number of patient whose hospitalization prolonged due to ADRs.

[†]Patients' hospitalization prolonged in number of days.

[§]Average hospitalization prolonged due to ADRs.

The responses received to validate success factors and performance indicators to finalize PFAQ via Delphi panel were found to be higher 58.75% in our study in contrast to similar study carried out in Malaysia, where only 18% panel members participated to determine the perception of physicians toward ADR reporting (Alshakka *et al.*, 2013).

Despite, many national and international drug safety reporting schemes are in place, we are far behind in reporting of ADRs. One systematic study carried out in Europe suggests that the lack of knowledge, time, interest, and uncertainty about causality is the major cause in under-reporting of ADRs (Hopf *et al.*, 2016). Few government and privately funded agencies have found out that, two-thirds of the 411 (65.8%) respondents had no knowledge of the ADR reporting system. A very small percentage of respondents 101 (16.2%) had ever reported ADRs in their professional career. This kind of studies justifies why such drug safety reporting network and training platforms should be implemented in each hospital to improve the rate of ADR reporting in the hospital (Mulatu, 2014). Even results of the final PFAQ survey among HCPs reveals that, HCPs are more informed (52%), have better accessibility (54.1%), more aware (52%), have gone through appropriate training (56.2%), have better communication with PSUR team and work station (54.1%), and there is an overall improvement (68.75%) in the drug safety reporting and monitoring system during the phase 2 study period since the PSUR system implemented in our hospital (phase 1) as shown in Figure 1.

ADR reporting rate for selected three drugs from published literatures in Indian health-care setup was found to be in the range of 3% to 6% for amlodipine, 5% to 10% for furosemide, and 3% to 10% for risperidone (Aqil *et al.*, 2006; Khurshid *et al.*, 2012; Lihite *et al.*, 2017; Piparva *et al.*, 2011). A similar pattern of ADR reporting was found in our study for selected drugs as well (Fig. 2). Prior to 6-month ADR reporting study carried out at medicine ward of our hospital reveals total 317 (22%) ADRs were reported from 1,438 patients (Thiagu, 2011). This finding contradicts the result outputs of our study reported from the same hospital. We found the ADR reporting rate for selected three drugs was 4.6% prior to PSUR system implemented in the hospital and rose to 7.87% post-PSUR implementation. The reason behind the difference in the ADR reporting rate might be due to, we had selected pool of patients, who were prescribed either of three selected drugs. Though, we have observed there is a significant increment in ADR reporting rate (75%) for amlodipine from medicine ward and furosemide (35%) from Nephrology ward since PSUR system implementation in the hospital (Fig. 4).

One systematic meta-analysis study carried out at Portugal endorses our work by suggesting that the projects included in their study which were using active promotional/interventional methods for ADR reporting have doubled the rate of ADR reporting compared with other projects which were using passive promotion of ADR reporting methods (Vaz *et al.*, 2016a; 2016b). A similar study was conducted in Malaysia to find out the impact of knowledge intervention on community pharmacist in ADR reporting. It was observed in the study, 76% participants were unaware of pharmacovigilance and ADR reporting. It has been found out in the study, ADR reporting

Table 6. ADR reporting rate pre and post PSUR system implementation.

#	Drugs	March to Nov 2013 (Before PSUR implementation)			December 2013 to August 2014 (After PSUR implementation)		
		Prescriptions (n)	ADRs (n)	ADR report rate (%)	Prescriptions (n)	ADRs (n)	ADR report rate (%)
1	Amlodipine	508	10	2	432	20	4.62
2	Furosemide	702	40	5.69	688	62	9
3	Risperidone	245	15	6.12	252	25	10
4	Overall reporting rate	1455	65	4.6	1372	107	7.87

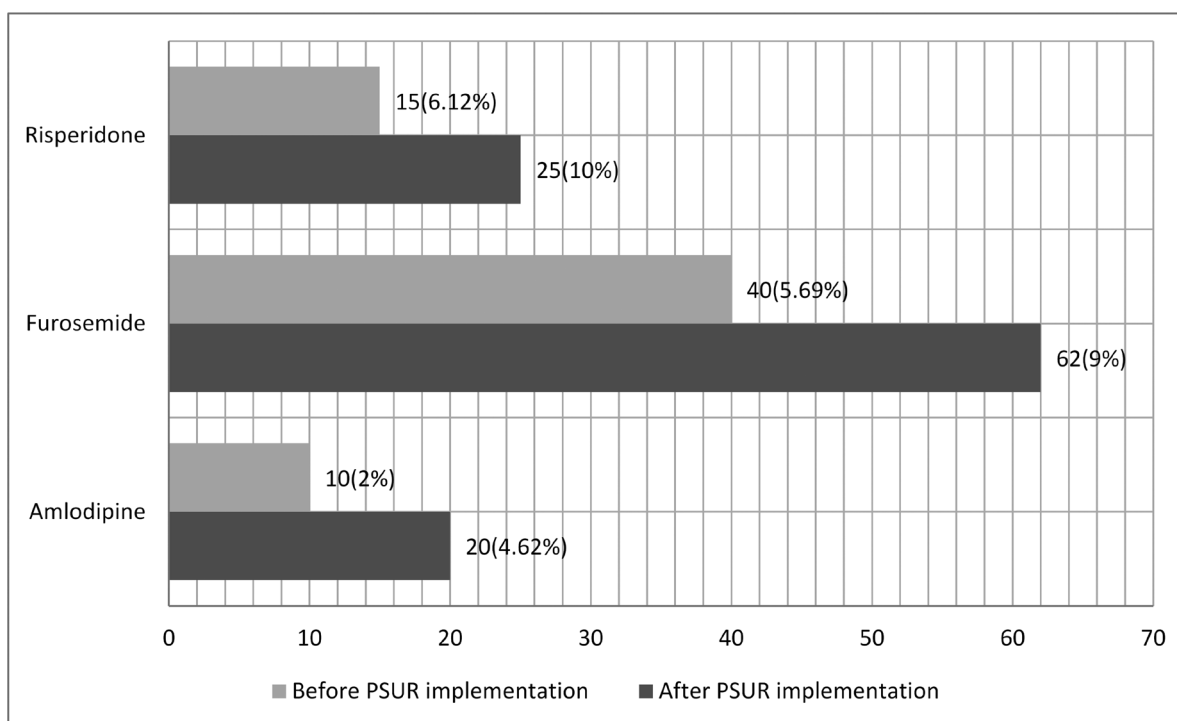
rate among the surveyed pharmacists was very less (9%) and ADR reporting rate was found to be significantly increased after their participation in the study (Elkalmi *et al.*, 2011). The similar trend of increment of ADR reporting rate observed in our study for selected three drugs when routed through well-administered PSUR system (Fig. 2).

One related study of perception on ADR reporting among physicians, in government and private hospitals in Kuwait, reveals that the private physicians demonstrated a better knowledge of PV basics (75.8% vs. 65.3%; $p = 0.001$) and practice (75.2% vs. 64.8%; $p = 0.002$) (Alsaleh *et al.*, 2017). A similar study carried out in Kolkata, India found that 92% physicians in hospital settings believed that reporting ADRs is necessary and would benefit the patient. While, 74% physicians have a belief that ADR reporting is a professional obligation for doctors. That means, HCPs are aware about ADR monitoring and reporting process but the lack of implementation of such program of drug safety reporting network in health care setup resist them to report ADRs (Kamtane *et al.*, 2012).

CONCLUSION

The current study supports the critical importance of implementing drug safety network and periodic safety update reporting systems, particularly in Indian hospitals. We observed that the rate of ADR reporting increased by 68% from different wards of the hospital for the test samples when ADR monitoring was conducted by trained HCPs and routed through a well-administered PSUR system. All the wards of the hospital have been sensitized and alerted toward ADR reporting.

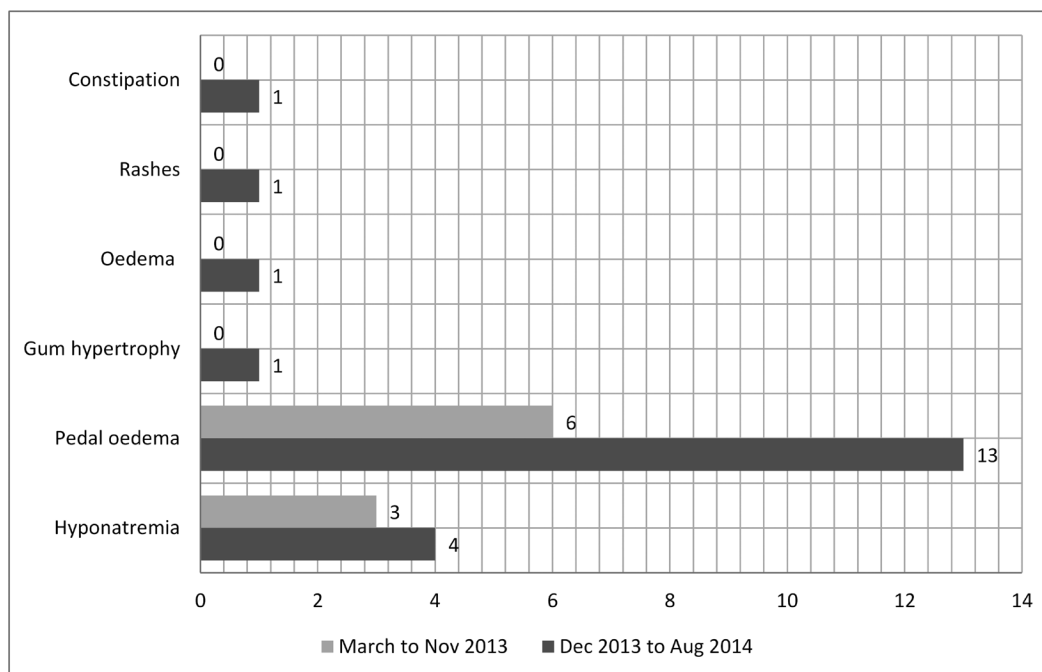
This study illustrates how a formal drug safety reporting network can be established by redeploying the existing resources without additional capital investments/human resources in training or new job positions. Implementation of PSUR system in the teaching hospital has greater long-term benefits because it enhances participation of all players across the healthcare team, including students. Being linked to the educational program, such a system also helps spread awareness among the HCPs on ADR reporting and analysis.



Phase 1 (Before PSUR system implementation, March to Nov 2013)

Phase 2 (After PSUR system implementation, Dec 2013 to Aug 2014)

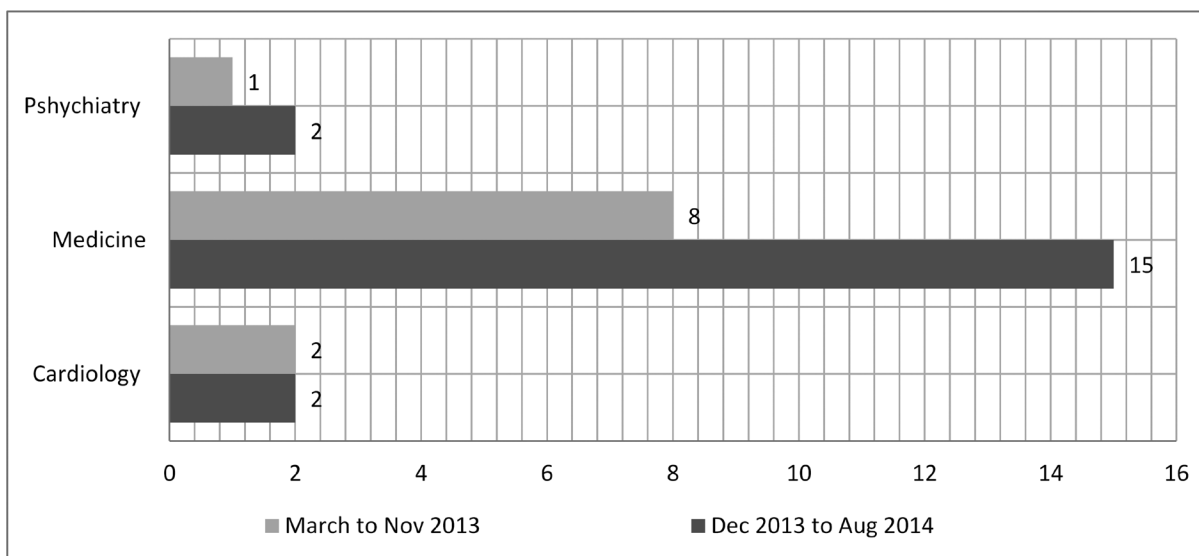
Fig 2. ADR reporting rate pre and post PSUR system implementation for selected three highly prescribed drugs, risperidone, furosemide and amlodipine.



Phase 1 (Before PSUR system implementation, March to Nov 2013)

Phase 2 (After PSUR system implementation, Dec 2013 to Aug 2014)

Fig 3. Rate of ADR reporting by MedDRA preferred terms pre and post PSUR system implementation for Amlodipine.



Phase 1 (Before PSUR system implementation, March to Nov 2013)

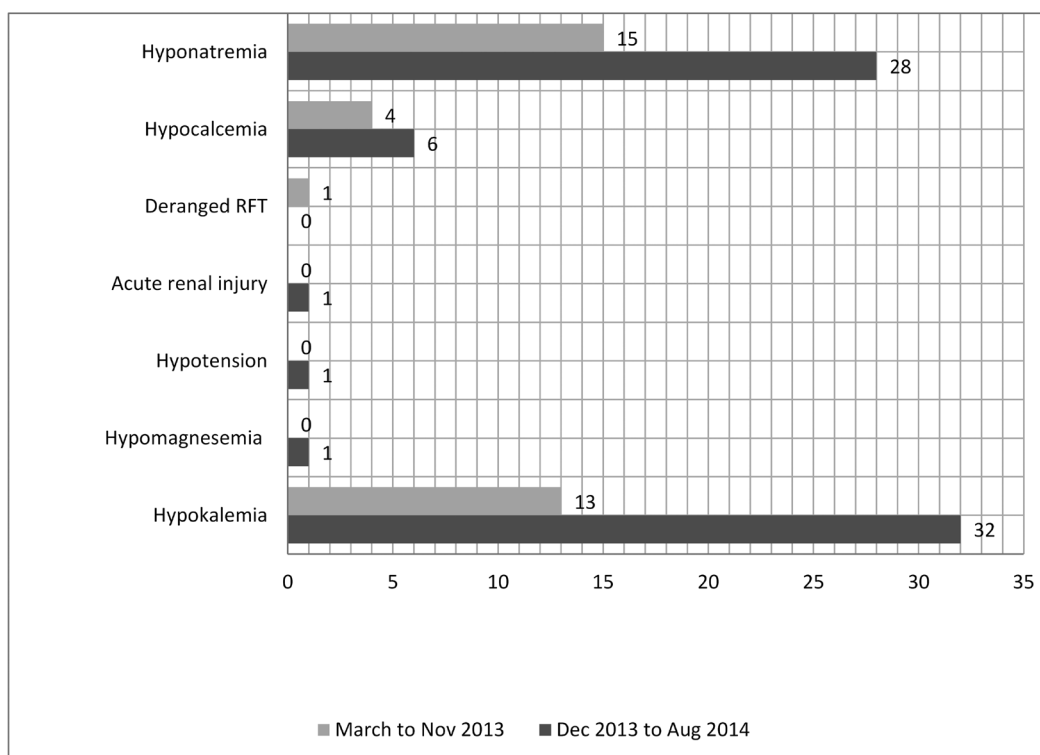
Phase 2 (After PSUR system implementation, Dec 2013 to Aug 2014)

Fig 4. ADR reporting by Ward pre and post PSUR system implementation for Amlodipine.

PSUR system implementation also increases awareness about the incidence, severity, causality, preventability, and risk-benefit ratio of medications. Reporting unexpected/unreported ADRs is critically important for ethnically diverse countries such as India, which does not generate many clinical data because of fewer formal clinical trials and even fewer new drug launches.

PSUR reporting can generate accurate drug safety surveillance data and assist DCGI in taking decisions on safety-

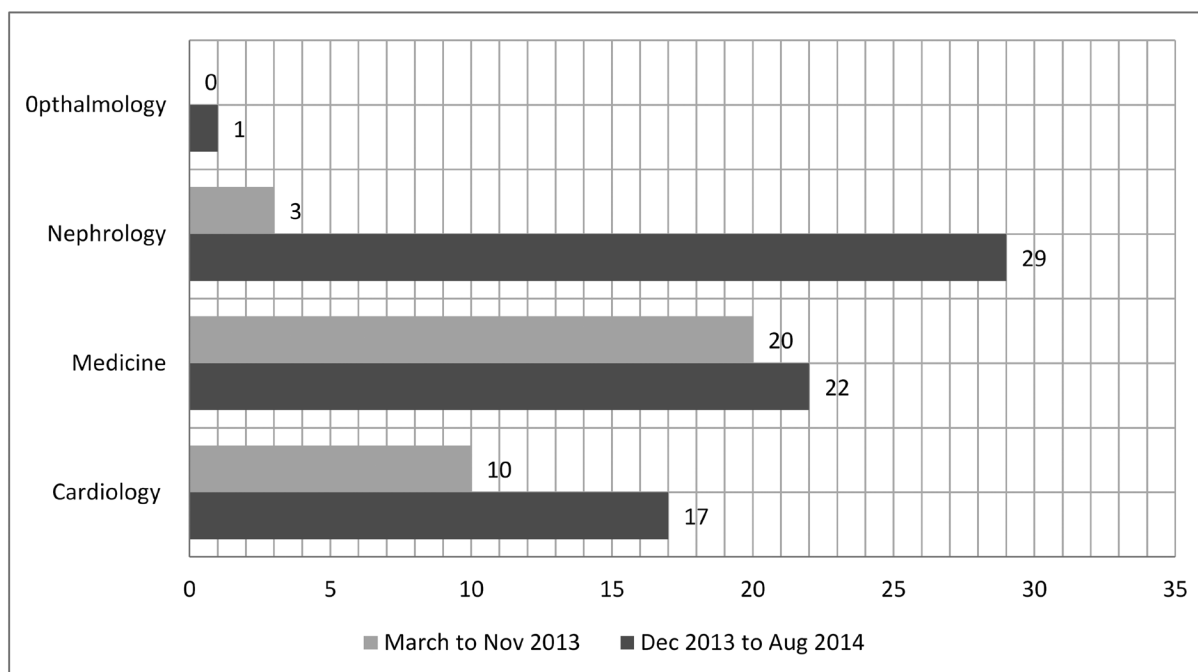
related issues of newer drugs and validate the accuracy of drug safety data (PSURs) submitted by MAHs. The PSUR data submitted by MAHs is inaccessible and confidential because pharmaceutical industries are reluctant to disclose results which adversely impact their marketed products. PSURs generated by teaching hospitals are less likely to be tainted by conflicts of interest and will provide more accurate data accessible to all including the lay public. The dissemination of PSUR through newsletters, publications, and so on adds value to the exercise.



Phase 1 (Before PSUR system implementation, March to Nov 2013)

Phase 2 (After PSUR system implementation, Dec 2013 to Aug 2014)

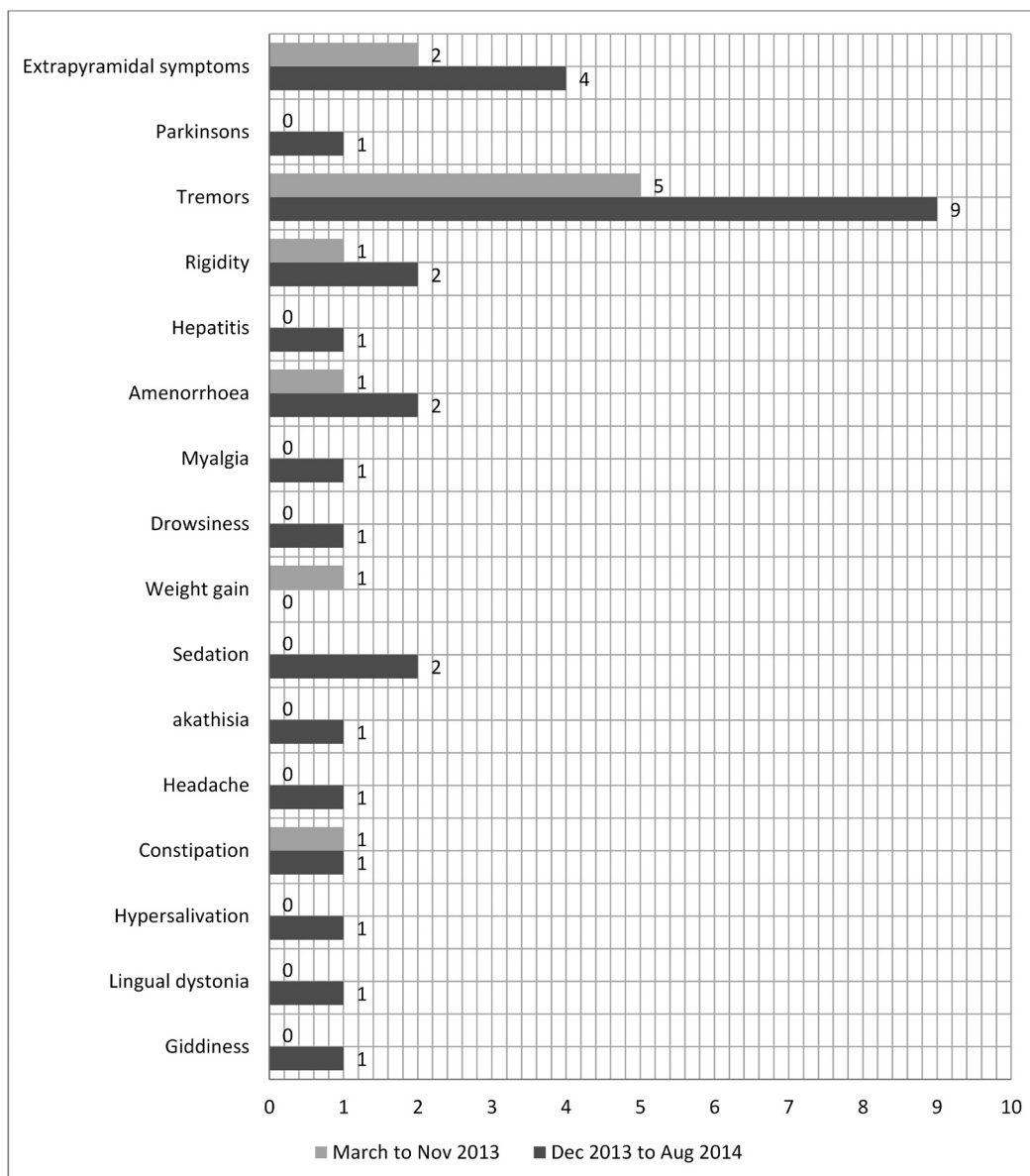
Fig 5. Rate of ADR reporting by MedDRA preferred terms pre and post PSUR system implementation for furosemide.



Phase 1 (Before PSUR system implementation, March to Nov 2013)

Phase 2 (After PSUR system implementation, Dec 2013 to Aug 2014)

Fig 6. ADR reporting by Ward pre and post PSUR system implementation for furosemide.



Phase 1 (Before PSUR system implementation, March to Nov 2013)

Phase 2 (After PSUR system implementation, Dec 2013 to Aug 2014)

Fig 7. Rate of ADR reporting by MedDRA preferred terms pre and post PSUR system implementation for risperidone in Psychiatry ward.

STUDY LIMITATIONS

There were only three drugs selected to assess the impact of newly implemented PSUR systems in terms of ADR reporting rate pre- and post-PSUR system implementation; which couldn't predict the success of implemented PSUR system in the hospital. However, later, 11 drugs launched in the year 2011 in India were included for ADR reporting under this PSUR system and we would be presenting further study results from this program shortly.

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CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

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