



## Research Article

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## Evaluation of completeness of adverse drug reaction case reports published in biomedical Journals: A preliminary analysis

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### Abstract

**Background:** Adverse drug reaction (ADR) case reports help to identify potential risks associated with the use of the drug especially serious rare adverse effects, which are often missed during clinical trials. When properly documented, they alert clinicians towards any untoward effect of drugs and help them to make important decisions concerning the health of their patients. However, the completeness of published ADR case reports varies greatly. The lack of relevant details can be misleading & limit their value in clinical practice. **Methods:** We downloaded 80 ADR case reports published during a period of 1 year from September, 2014 – September, 2015, from 4 biomedical journals (20 from each journal) and analyzed them for their completeness using the International Society of Pharmacoepidemiology (ISPE) & International Society of Pharmacovigilance (ISOP), 2007 guidelines. **Results:** We found that most of the patient – related & ADR – related details were adequately reported (>90%) whereas the title, most of the drug related details & highly desired parameters were reported poorly (< 90%). The completeness of ADR case reports ranged from 10/17 to 16/17 for required parameters & from 2/13 to 11/13 for highly desired parameters. **Conclusions:** Our study highlights the deficiencies in published ADR case reports, we suggest the researchers to follow the ISPE & ISOP guidelines while writing an ADR case report & the journal editors to incorporate minimum publishing requirements for publishing ADR case reports to gain the most out of them.

**Keywords:** Drug safety, Pharmacovigilance, ADR.

### INTRODUCTION

An adverse drug reaction case report refers to a scientific publication that is written by a health care professional who suspects a causal relationship between a drug and an adverse drug reaction (ADR) [1].

In the evidence based medicine era; systematic reviews, meta-analysis & randomized controlled trials are favored more than case reports [2]. Nevertheless, case reports should be published, as they form an important part of post-marketing safety surveillance of drugs. Out of all the primary published work on ADR's, 30% was contributed by case reports, 43% by randomized & non randomized trials, 1% in the form of meta-analysis & rest by other modes of scientific communications (animal experimental studies, observational studies, editorials, official statements etc.) [3].

ADR case reports also help to identify potential risks associated with the use of the drug especially, serious rare ADR, which are often missed during clinical trials [4]. Owing to the increased risk of cardiovascular events, Rosiglitazone an oral hypoglycemic agent, approved in India in 2000, and Valdecoxib an anti-inflammatory drug approved in 2002 were withdrawn from Indian market in 2010 & 2005 [5-7]. Such rare serious ADRs ought to be notified to competent authority and also published in a biomedical journal as an ADR case report to create awareness amongst clinicians [4, 8].

When properly documented, these reports alert clinicians towards any untoward effect of drugs and help them to make important decisions concerning the health of their patients. However, the completeness of published ADR case reports varies greatly. Lack of relevant details can be misleading thereby, limiting their value in clinical practice [4]. Hence, we carried out this study to evaluate the completeness of ADR case reports in biomedical journals according to the criteria laid down by the standard guidelines.

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## MATERIALS AND METHODS

For this preliminary work, we decided to collect 20 case reports each from 4 commonly accessed biomedical journals (3 Indians and one international) published during a period of one year (September, 2014 – September, 2015). This way, we collected a total of 80 case reports.

We selected 3 commonly accessed Pharmacology journals available in India. All of these journals are Open access and are subjected to peer review process, out of these 3 journals, two are PubMed indexed i.e. Indian Journal of Pharmacology and Journal of Pharmacology and Pharmacotherapeutics (JPP) while one journal is non -PubMed indexed, i.e. Indian Journal of Basic & Clinical Pharmacology (IJBCP).

To avoid bias and for better comparison, we decided to include a widely accessed, open access, peer reviewed, International, PubMed indexed journal i.e. British Medical Journal (BMJ) Case Reports.

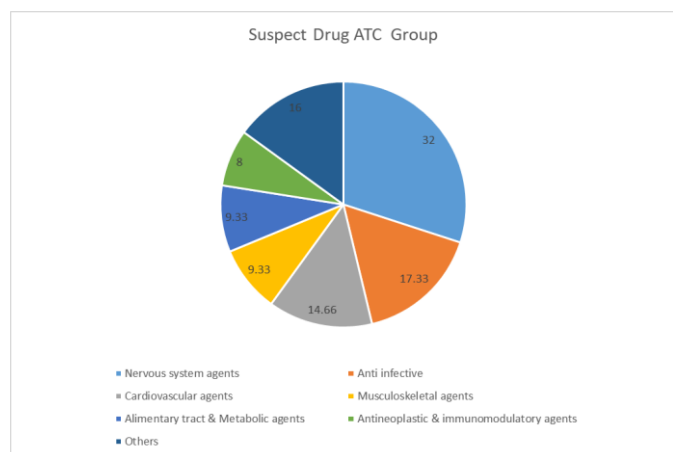
These ADR case reports were then analyzed by two investigators independently and assessed for their completeness using the guidelines laid down by International Society of Pharmacoepidemiology (ISPE) & International Society of Pharmacovigilance (ISOP) in 2007 [9].

### Statistical Analysis

Data was represented using numbers and percentages wherever necessary.

## RESULTS

In our study, 75 different drugs were suspected to have caused the ADR's. According to the Anatomical Therapeutic Chemical (ATC) classification these drugs belonged to 14 different ATC groups details of which are shown in fig.1 [10].



There were 17 required parameters and 13 highly desired parameters as proposed by ISPE & ISOP guidelines. We divided the 17 required parameters of the ISPE & ISOP guidelines into patient- related, drug related & ADR related parameters. The reporting frequency of various parameters in different journals is given in Table 1, 2, and 3 respectively.

**Table 1:** Frequency of reporting Required- Drug Related Parameters

No. Parameters	IJP n=20	JPP n=20	IJBCP n=20	BMJ n=20	Total n=80 (%)
1 Generic name	20	20	20	19	79 (98.7)
2 Proprietary name	1	1	1	1	04 (5)
3 Dosage	15	18	17	17	67 (83.7)
4 Duration of therapy	13	18	18	15	64 (80)
5 Therapy duration before adverse event	18	18	18	17	71 (88.7)
6 Off label/labelled use	2	2	13	5	22 (27.5)

**Table 2:** Frequency of reporting Required- Patient Related Parameters

No Parameters	IJP n=20	JPP n=20	IJBCP n=20	BMJ n=20	Total n=80 (%)
1 Age	20	20	20	19	79 (98.7)
2 Sex	20	20	20	20	80 (100)
3 Current symptoms being treated with suspect drug	20	19	20	20	79 (98.7)
4 Medical history	16	20	20	19	75 (93.7)
5 Physical examination findings	20	19	19	20	78 (97.5)
6 Patient disposition	12	7	11	16	46 (57.5)

**Table 3:** Frequency of reporting Required- ADR Related Parameters

No. Parameters	IJP n=20	JPP n=20	IJBCP n=20	BMJ n=20	Total n=80 (%)
1 Concomitant therapy contribution	13	16	18	13	60 (75)
2 ADR description	20	19	20	19	78 (97.5)
3 Evidence of causality	20	19	20	19	78 (97.5)
4 Previous report on ADR	19	20	20	20	79 (98.7)

The title, which was one of the required parameters was appropriate in 66/80 (82.5%) of the ADR case reports (16/20 for IJP, 19/20 for JPP, 18/20 for IJBCP, 13/20 for BMJ). While the ADR was not mentioned in 1/80 (IJBCP), the suspect drug name was not mentioned in 13/80 (16.25%), in 9/13 (69.23%), at-least the class to which the suspect drug belonged was mentioned. The reporting frequency of highly desired parameters in different journals is shown in Table 4.

**Table 4:** Frequency of reporting Reporting of highly desired parameters

No. Parameters	IJP n=20	JPP n=20	IJBCP n=20	BMJ n=20	Total n=80 (%)
1 Weight	3	1	3	0	7 (8.7)
2 Duration of illness	9	12	7	15	43 (53.7)
3 Prior exposure to drug class	7	8	6	8	29 (36.2)
4 Underlying risk factors	9	10	12	11	42 (52.5)
5 Baseline lab values	6	3	3	1	13 (16.2)
6 Status several months after the ADR	6	2	7	14	29 (36.2)
7 Start & stop dates	0	0	3	0	3 (3.7)
8 Route of administration	11	11	13	14	49 (61.2)
9 First dose -event interval	18	18	17	16	69 (86.2)
10 Last dose -event interval	0	3	3	0	6 (7.5)
11 Procedure to diagnose	11	12	19	19	61 (76.2)
12 Biological plausibility	19	17	18	18	72 (90)
13 Assessed competing explanations	18	18	20	18	74 (92.5)

The completeness of the ADR case reports with respect to required parameters, ranged from 10/17 (58.8%) to 16/17 (94.1%), for highly desired parameters from 2/13 (15.4%) to 11/13 (84.6%) and the average completeness being 13.8/17 (81.4%) and 6.2/13 (47.7%). The range and average completeness of individual journals is given in Table 5.

**Table 5: Range of Completeness**

Parameters		IJP	JPP	IJBCP	BMJ
Required n=17	Range	11-15	10-16	12-16	10-16
	Average	13.3	13.7	14.6	13.6
Highly Desired n=13	Range	4-8	2-9	4-11	4-9
	Average	5.9	5.7	6.6	6.5

## DISCUSSION

Publishing ADR case reports in biomedical journals according to the standard guidelines is essential to suspect a causal relationship between the drug and the ADR. Moreover, this is very important clinically as it can affect the prescribing pattern [8].

In our study we found that, amongst the required parameters, majority of the researchers have described most of the patient & ADR related details adequately (>90% reporting) (Table 1 & 3) and this finding is well supported by the studies done by Impicciatore & Mucci<sup>8</sup> and Palaian *et al* [11]. However, when it came to reporting drug related details in the ADR case report, we felt that the researchers largely fell short. Completeness of drug related details is an essential step as inadequately and incompletely reported information could be detrimental for prescribing trends among health care professionals.

Amongst the drug related details, proprietary name of suspect drug was the least reported parameter (5%). In the study by Impicciatore & Mucci [8], the proprietary name was not mentioned in 11%. Same drug products produced by different drug manufacturers, may differ in their bioavailability, seen commonly with drugs having narrow therapeutic index e.g. in case of antiepileptic drugs like phenytoin (slight changes in plasma concentration may lead to therapeutic failure or toxicity on below and above the range of plasma concentration, respectively), those who have unstable molecule [12] or when different excipient is used for manufacturing, as was seen in the case of phenytoin toxicity outbreak in Brisbane, Australia, 1968 following a change of excipient from calcium sulphate to lactose [13]. Knowing the proprietary name in such cases would give a better insight over the suspected cause of the occurrence of an ADR.

Suspect drug dosage, plays an important factor in determining whether the ADR is a Type A reaction (augmented reaction), that depends on the dosage of the drug. In a study done by Routledge *et al* [14] this incidence was estimated at 80% of all ADRs occurring in an hospital, knowing the drug dose that is causing an ADR can help prevent it in the future by optimizing to a safe dose. Impicciatore & Mucci [8] and Palaian *et al* [11] showed that 15% & 22.2% researchers had failed to report suspect drug dosage, which is consistent to our study finding of 16%. Knowing about the doses leading to a particular ADR is of great importance because it can give a new range of dose leading to the ADR that might be useful in formulating new treatment guidelines e.g. changing the dose in a particular disorder. Moreover with the knowledge of pharmacogenomics, variation in inter-individual response to a different therapeutic doses of drugs, and also the effect of ethnicity and gender demands the proper information of dose leading to an ADR.

72.5% researchers failed to report whether the use of the drug was an off label or a labelled use. Off label uses expose the patient to unknown health risks as these uses have not been evaluated scientifically, this happened in the case of Fenfluramine, which had been approved for short-term use in obesity, its off label long-term combination use with phentermine caused valvular heart diseases [15].

Amongst the ADR related parameters, 42.5% researchers failed to report patient disposition, i.e. the outcome of the patient owing to the

ADR, whether there is presence or absence of death, life-threatening circumstances, hospitalization, prolonged hospitalization, or significant disability<sup>9</sup> & 25% failed to report the assessment of concomitant therapy contribution.

Although the ISPE & ISOP guidelines [9] have not specified a structure for the title of an ADR case report, we decided to evaluate the completeness of the title of the ADR case reports on the basis of mentioning the ADR & suspect drug name. We found that the title was incomplete in 14/80 (18.5%) ADR case reports, majority of which were incomplete because they had failed to mention the suspect drug name (13/80). A complete title would make it easier for researchers to retrieve the publication from the database.

The ISPE & ISOP guidelines have urged the researchers, to wherever possible mention both required (tier 1) & highly desirable parameters (tier 2) to promote a clear & structured differential diagnosis for the event [9]. However, we found that the average completeness of each article with regards to required parameters was 81.4% and with regards to highly desired parameters was only 47.7%. All highly desired parameters except discussing the biological plausibility and assessment of competing explanations were poorly reported (<90%) (Table 4).

A seemingly high percentage of researchers, 39% in our study & 63% in the study by Impicciatore & Mucci [8] failed to report the route of administration of the suspect drug. ADR may be related to a specific route of administration, like in the case of vincristine which caused paralysis and death in children when it was administered intra-theal, while it is still safely used in the treatment of cancer by intravenous route [16]. Not knowing this piece of information can tarnish the goodness of a valuable drug. The poor reporting of route by researchers may in part be attributed to the fact that the ISPE & ISOP guidelines have mentioned the suspect drug route to be a tier 2 information or a highly desired parameter and not a required one [9].

The patient outcome & status several months after the ADR parameters were better reported in BMJ case reports. This can be due to the fact that journal has specifically urged the researchers to include follow up information & provided them with an option to come back later and update the case report with the progress or outcome of the ADR with the view of making the case reports as valuable as possible [17].

From Table 5, we can see that with respect to completeness of ADR case reports there is an intra-journal variation. This could be attributed to the lack of strict guidelines for publishing an ADR case report by individual journals. 3/4 journals in our study (IJP, JPP & BMJ-case reports) have specified general instructions (presentation, format viz. introduction, case history, discussions, references, and acknowledgement) for the submission of a case report. But none of the 4 journals had given specific instructions for submitting an ADR case report [18-20]. ISPE & ISOP guidelines were published & made available for use since 2007 [9]. Even after several years of its existence, the completeness of ADR case reports still remains poor. A restricted word limit for publishing an ADR case report in 3/4 of the journals (IJP, JPP & BMJ-case reports) selected by us, could also be one of the hindrances in furnishing of all relevant details by researchers. The average completeness with respect to both required & highly desired parameters in between the peer reviewed open access journals, whether the journal was PubMed indexed or not, Indian or International, took publication fee or not, was found to be similar.

ISPE & ISOP guidelines divides the key information to be reported in an ADR case report into three tiers, tier 1- required, tier 2- highly desirable, tier 3 – if relevant [9]. In this study we have only focused on tier 1 & 2 parameters as, tier 3 deals with deciding the relevance, which becomes subjective, and the relevant factors may change with time as we learn more about the ADR [21]. Thus, if there were a proper

checklist, like the CONSORT-2010 checklist for randomized controlled trials instead of a guideline, it would be easier for researchers to adopt it for writing & for editors for reviewing ADR case reports for publishing.

A small sample size of 20 case reports/ journal and inability to report information on the wide spectrum of biomedical journals available globally are our study limitations. However, we took this work as a preliminary effort to highlight the need of reporting ADR case reports in a standardized format, so that the information can be utilized more efficiently by the health care professionals.

## CONCLUSION

In view of the deficiencies highlighted by our study in reporting suspect drug related information & tier 2 key information in ADR case reports according to the ISPE & ISOP guidelines, we suggest the researchers to follow the guidelines while writing an ADR case report & the journal editors to incorporate minimum publishing requirements for ADR case reports to report the most authentic and validated information.

## Conflicts of Interest

The authors declare that there is no conflict of interest.

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