ANALYSIS AND CONTRIBUTION OF PHARMACEUTICAL DRUG PACKAGES AND PACKAGE INSERTS TOWARDS THE DEVELOPMENT OF PHARMACOVIGILANCE SYSTEM IN PAKISTAN.

Halima Sadia[1*], Hina Rehman[2], Safila Naveed.[3]

ABSTRACT

Introduction: Safe use of a drug is promoted via accurate information. The most accessible form of information for patients regarding drugs is the drug package and package insert, especially, in case of adverse event. Reporting of adverse drug reaction is an important element of pharmacovigilance. **Objective:** The aim of the study was to analyze the pharmaceutical drug packages and their package inserts available in Pakistan, and identify their contribution towards the development of pharmacovigilance system in Pakistan. **Settings and Design:** Collection of drug packages and package inserts from various pharmacies of Karachi. **Methods:** Two hundred and fifty two drug packages and package insert of local (n=178) and multinational (n = 74) origin were randomly selected, based on their availability in Pakistan. Each of the drug package and package insert was evaluated as per the criteria laid down by the Drug Regulatory Authority of Pakistan (DRAP). Additionally, they were also analyzed for the presence of the information regarding adverse drug reaction (ADR) reporting.Statistical analysis used**:** SPSS Version 20.0. **Results:** Information regarding dosing in special population, clinical pharmacology, patient counseling information etc. was not found in majority of the package inserts. ADR reporting information lacked in both the drug packages and inserts. Only 3% (n = 9) of the drug packages and 0.8% (n = 2) of the inserts had included the reporting information. The reporting information was shared by multinational pharmaceutical companies. None of the local pharmaceutical companies had shared the ADR reporting information. **Conclusion:** Majorly, the drugs packages and to some extent the package inserts comply with the rules. However, no information regarding ADR reporting was found. Hence, it is recommended that measures such as provision of a toll-free number would encourage ADR reporting among the drug consumers.

Key-words: ADR reporting, Drug package, Package inserts, Pharmacovigilance, Pakistan

1. Department of Pharmacy Practice, Faculty of Pharmacy, Jinnah University for Women.
2. Department of Pharmacy Practice, Institute of Pharmaceutical Sciences, Jinnah Sindh Medical University.
3. Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Jinnah University for Women.

*__Corresponding Author__: Halima Sadia, Jinnah University for Women, Nazimabad5C, Karachi

E-mail address: halimasadia093@gmail.com

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INTRODUCTION

The effective and safe use of a drug can only be accomplished, if reliable and accurate drug information is provided [1]. Relief of symptoms and reduced number of medication errors is directly linked with the authentic drug information and its smooth supply [2].

From a patient's perspective, the prime source of information about how, when and why to take the medicine and other instructions regarding medicine use is the printed information accompanying the drug product[3]. This includes the immediate or primary drug packaging, the external package and also the inserts and leaflets which accompany the product[4]. The drug package inserts or pharmaceutical package inserts serve as an authentic source of drug information for all the drug molecules especially, the new ones. For any drug which is under consideration they may act as the first hand information[5].The inserts are also of a great help in developing countries where prescribers lack easy access to independent medication information resources. In such circumstances, medication information is only achievable by means of promotional activities of the pharmaceutical companies. In general, pharmaceutical package inserts represents a useful and easily accessible source of information about the medicine. They offer the advantage of convenient readability and can be complemented and reinforced along the verbal information provided by the health care providers[6].

Apart from the stability and integrity of the medicine, pharmaceutical packaging also serves as an information medium. The information provided by the drug package is just not limited to the patients but is also beneficial for the

medical professionals i.e. pharmacists, prescribers and nurses at the time of drug delivery [7].

The information provided on the pharmaceutical package (labeling and insert) would be beneficial for the patient only if, it is clear as it is the chief source of information when no professional is available for advice. It is of utmost important in scenarios when the patient encounters any drug related morbidity or mortality including adverse drug reactions (ADRs).Adverse drug reactions are a global costly problem. They impose a fiscal burden to the society's health care system. It is one of the common reasons behind patient hospitalization.

A system that deals with the reporting, monitoring and prevention of adverse drug reactions is of utmost importance. All this is governed by the umbrella term pharmacovigilance which deals with the detection, determination, evaluation and prophylaxis or preventive measures in association to any drug or medicine for its unusual adverse events [8]. The pharmacovigilance serves as a fundamental component to ensure safety of the pharmaceutical care. The discipline is well established in the developed countries. However, the state of pharmacovigilance is still in infancy in Pakistan [9, 10]. Although, the pharmacovigilance system has been introduced by the Drug Regulatory Authority of Pakistan (DRAP), yet, the concept of pharmacovigilance and access to it still remains a question for the common man.

AIM OF THE STUDY

The current study aimed to assess the information provided by the pharmaceutical drug packages and package insertsin Pakistan, as well as their contribution towards the development of pharmacovigilance.

ETHICS APPROVAL

The study was approved by Institutional Review Board (IRB) at Jinnah University for Women, Karachi.

METHODS

Collection of drug packages and package insert

Different drug packages and package inserts were randomly obtained from various pharmacies of Karachi, Pakistan from October 2018 to November 2018.

Criteria for evaluation of drug packages

The drug packages were analyzed as per the criteria laid by the Drug Regulatory Authority of Pakistan (DRAP) in Drug Labeling and Packaging rules 1986. Following criteria was used for the analysis: (a) Registered name of the drug (b) Generic name of the drug (c) The chemical name, of each active ingredient of a drug with weight or measure in metric system (d) The name and address of manufacturer (e) The drug manufacturing number (f) The drug registration number (g) Expiry date (h) Urdu version of the name (i) The distinctive batch number, date of manufacture, and the maximum retail price. In addition, the packages were also analyzed for the presence of ADR reporting number on the drug package/container.

Criteria for evaluation of package inserts

The package inserts were analyzed as per the Food and Drug Administration (FDA) criteria. The package inserts were examined for: (1) Legibility (2) Approved generic name of active ingredient (3)Therapeutic class (4) Content of active ingredient per dosage form (5) Boxed warning (if any) (6) Therapeutic indication (7) Dosage form and strength (8) Posology and method of administration (9) Contraindication (10) Special warning and precautions (11) Drug interaction (12) Pregnancy and lactation (13) Pediatric and geriatric indications (14) Use in special population (15) Drug abuse and dependence (16) Effect on ability to drive or operate machine (17) Adverse effect (18)Pediatric dose (19) Clinical pharmacology (mechanism of action, pharmacodynamics, pharmacokinetics) (20) Overdose (21) Creatinine clearance (22) Antidote for overdose (23)Storage information (24) Clinical studies (25) Patient councellinginformation (26) Shelf life (27)Recent major changes (28) Date on which information was last updated (29) For more information (30) Retail price of the drug (31) Name and address of manufacturer (32) Contact details for reporting any ADR (33) References.

Evaluations were made on a "yes" or "no" basis with "yes" meaning the information was provided and "no" meaning no such information was provided.

Statistical Analysis

All the data was extracted twice to minimize any chance of error. The data has been statistically analyzed using Statistical Package for Social Sciences (SPSS Version 20.0).

RESULTS

A total of 252 samples were collected from different pharmacies and analyzed of which 29.3% (n=74) were from multinational pharmaceutical companies while the remaining 70.6% (n=178) from pharmaceutical companies of local origin.

Analysis of drug packages

Of the drug packages analyzed, all were found to be compliant with the Drug Labeling and Packaging Rule 1986. However, information on reporting any adverse event associated with the drug was found in only in 3% of the drug package. No pharmaceutical company of Pakistani origin had shared any information regarding ADR reporting (Figure 1).

Analysis of package inserts

Majority of the package inserts had information regarding generic name, content of active ingredient, dosage form, strength and name and address of manufacturer but lack in any special warnings, use in special population, patient counseling information etc (Table 1).

In contrast to the 3% of the drug packages that provided information for reporting ADR, only 2 package inserts (0.8%) had mentioned any contact details for reporting any adverse event caused by the drug. However, same pattern was

observed regarding pharmaceutical companies. The 0.8% package inserts belonged to multinational pharmaceutical company (Figure 2).

DISCUSSION

The pharmaceutical drug package and the pharmaceutical package insert contain information for the consumer or the patient which is related to the specific medication or the class of drugs prescribed.This information serves as the most readily and easily accessible form of written information on drugs for the patients. The information provided in the pharmaceutical drug package and insert is written with a perspective that it is easily understood by the general population[11]. The information is also regularly updated, as and when new and relevant data related to preclinical and clinical studies is available.

The information to be included in the drug packages or inserts varies considerably throughout the globe. In United States of America (USA), FDA (Food and Drug Administration) governs the packaging and labeling of pharmaceutical products. The information in the drug package and insert in the European region is in accordance to the European Medicine Agency (EMA)[4].

In Pakistan, the Ministry of National Health Services Regulation and Coordination is responsible for the regulation of healthcare, where, the regulation of pharmaceuticals is governed by the Drug Regulatory Authority of Pakistan (DRAP)[12]. The guidelines for the packaging of finished drugs, style of labeling, labeling of the drug for external use, labeling of the drug for internal use, labeling of the drugs for government supply, labeling of physician samples, use of letters to indicate specifications and labeling of sterile and non sterile products are described in the Drug Labeling and Packaging Rule 1986 as provided by the DRAP [13]. However, not much guidelines are available for the pharmaceutical package insert. Only a little is stated in the Schedule G of Drug (Licensing, registration and advertisement) Rules 1976 where the legibility and information pertaining to the rational use of drug are only highlighted[14].As a consequence of this, the package inserts have been evaluated in detail as per the FDA guidelines along with the Drug Rules 1976.

In Pakistan, not much work has been carried out in this regard. Ali et al have reported the compliance of the pharmaceutical packaging material as per the Drug Labeling and Packaging Rule 1986 where they evaluated 350 different packaging materials. Out of 350, more than 80% of the samples were found to be compliant with the drug rules [13]. In contrast to this study, our results revealed that almost all the packages whether of local or multinational origin, were compliant with the Drug Labeling and Packaging Rule 1986.[14]

Table 1: Package Inserts Evaluation

S.No	Criteria	Yes		No	
		n	%	n	%
1.	Legibility	237	94	15	6
2.	Generic name	239	94.8	13	5.2
3.	Therapeutic class	146	57.9	106	42.1
4.	Content of Active Ingredient	213	84.5	39	15.5
5.	Boxed warning(if any)	14	5.6	238	94.4
6.	Therapeutic indication	251	99.6	1	0.4
7.	Dosage form and strength	244	96.8	8	3.2
8.	Posology and method of administration	217	86.1	35	13.9
9.	Contraindication	238	94.4	14	5.6
10.	Special warning and precautions	233	92.5	19	7.5
11.	Drug interaction	204	81	48	19
12.	Pregnancy and lactation	203	80.6	49	19.4
13.	Pediatric and geriatric indications	98	38.9	154	61.1
14.	Use in special population	79	31.3	173	68.7
15.	Drug abuse and dependence	3	1.2	249	98.8
16.	Effect on ability to drive or operate machine	49	19.4	203	80.6
17.	Adverse effect	194	77	58	23
18.	Pediatric dose	103	40.9	149	59.1
19.	Clinical Pharmacology (Mechanism of Action, pharmacodynamics, pharmacokinetics)	172	68.3	80	31.7
20.	Overdose	155	68.3	80	31.7
21.	Creatinine clearance	34	13.5	218	86.5
22.	Antidote for overdose	56	22.2	196	77.8
23.	Storage information	231	91.7	21	8.3
24.	Clinical studies	29	11.5	223	88.5
25.	Patient councelling information	58	23	194	77
26.	Shelf life	40	15.9	212	84.1
27.	Recent major changes	4	1.6	248	98.4
28.	Date on which information was last updated	44	17.5	208	82.5
29.	For more information	30	11.9	222	88.1
30.	Retail price of the drug	3	1.2	249	98.8
31.	Name and address of manufacturer	245	97.2	7	2.8
32.	Contact details for reporting any ADR	2	0.8	250	99.2
33.	References	3	1.2	246	97.6

FIGURES

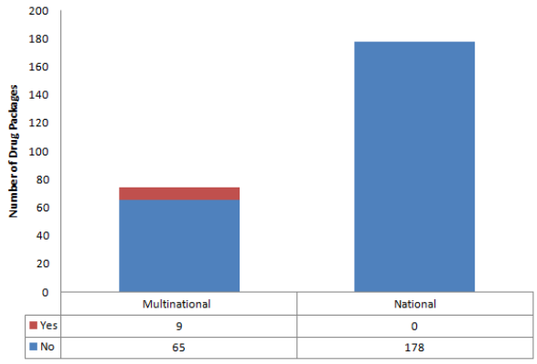

Fig 1: ADR Reporting Information on Drug Packages. Out of 252 drug packages only 3% (n=9) had information regarding ADR reporting while the remaining 97% (n=243) had no ADR reporting information. The 3% samples belonged to multinational pharmaceutical companies.

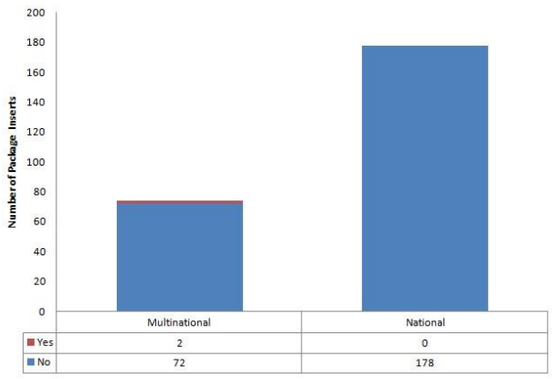

Fig 2: ADR Reporting Information on Package Inserts. Only 0.8% (n=2) package inserts had ADR reporting information. Similar to pharmaceutical packages, package inserts of multinational pharmaceutical companies had shared the ADR related information.

Complete and accurate drug information promotes safe and effective use of drugs. The primary source of information about medicines for patients is the pharmaceutical package insert. Negligence in this regard could lead to poor patient compliance. A study conducted by Arsalan et al reports that 9 out of 11 package inserts had 63 major errors along with 66 minor errors, while, the errors were not just limited to the local pharmaceutical companies [15]. Similarly, non-uniformity among the package inserts of all pharmaceutical companies in Pakistan has been documented by Naeem and Ahmed [16]. Our study revealed similar results.

The inserts lack in many aspects. There was unclear information about the dosing of drug in special populations, clinical pharmacology, etc. Out of a total of 252 package inserts only 1% had mentioned references on them where as only one fifth of the inserts provided the information regarding the update of the text with respect to time. No uniformity in the content was observed in all the samples.

Apart from the evaluation of the drug packages and the packaging insert as per the guidelines, they were also evaluated for information regarding ADR reporting. An adverse drug reaction increases the cost of the health care delivery. Not just the cost, they are also associated with increased risk of morbidity and mortality. ADRs should be promptly reported to measure and monitor the harm from the drug [17]. Knowledge about ADRs could significantly reduce its occurrence. However, along with the knowledge, reporting of ADRs is also essential. Even World Health Organization (WHO) has initiated various programs for the reporting of any adverse event caused by the drug. Monitoring of ADRs is a challenging problem and has eventually led to the emergence of the pharmacovigilance (PV). It monitors the safety related parameters and undesirable effects of drug throughout its lifecycle. Reporting of ADR is an essential component for efficient pharmacovigilance[18,19].

Underreporting of ADR is a widespread challenge in PV. The reasons behind underreporting from doctor's point of view includes lethargy, diffidence, feeling of guilt, lack of awareness about PV and insufficient training to identify ADRs. On the contrary, patient related reasons include failure to recognize ADRs or not knowing how to report an ADR [20]. The information provided in the drug package and package insert is the primary source of information in the non-availability of the medical professional. Of the 252 samples studied, only 3% had labeled on the drug

package while only 1% of the package insert had information regarding how to report an ADR by providing a toll-free number. The practice was observed only in the drug packages and package insert of multinational origin.

Unawareness about how to report an ADR is a major patient barrier in ADR reporting [21]. A study conducted by Syed at al revealed that the unavailability of the reporting forms and lack of pharmacovigilance centers/programs are key barriers for ADR reporting [22]. PV programs are implemented to provide the best care to the patient. Over the recent years, PV has been a lot in news in Pakistan. PV centers have been made at national and provincial level by the DRAP facilitating and encouraging people and healthcare professionals to report ADR. However, no such platform is provided for reporting any ADR.

Provision of a toll-free number encourages the ADR reporting [23]. With the advancement in the field of pharmacovigilance, efforts should be made to remove barriers in ADR reporting. An inclusion of a toll-free number on the drug packages or package insert to report ADR would significantly contribute towards patient safety and the regularization of pharmacovigilancesystem especially in a developing country like Pakistan where actual statistics about the death related to adverse drug events are yet not available.

CONCLUSION

Patient safety serves as the cornerstone of high quality health care. Accurate information about the drug and reporting of an adverse event promotes patient safety. In addition, development and implementation of pharmacovigilance is the need of the hour. Reporting of ADR significantly contributes to pharmacovigilance system in any country, especially in a country like Pakistan, where the emergence of pharmacovigilance system is still in infancy. Hence, it is recommended that measures such as provision of a toll-free number would encourage ADR reporting among the drug consumers.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to disclose.

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