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Quality of Medicine Information in Product Information Leaflets: A Retrospective Audit

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Abstract

Background: Nonstandard product information leaflets (PIs) may lead to medication errors. We assessed the completeness, and compatibility of, essential information against reference sources in selected PIs of medicines used in Sri Lanka. *Methods:* Hundred PIs each were used to assess completeness and compatibility of information, respectively. Availability of essential information was checked against drug regulations of the country. Clinical facts were matched against the British National Formulary and/or Australian Medicines Handbook for compatibility. PIs were categorized as "compatible" if all facts stated under each clinical information type were mentioned in at least one of the references; "partially compatible" if only some facts mentioned under each clinical information type were available in at least one of the references; and "totally incompatible" if none of the facts stated in each clinical information type were mentioned in both references. *Results:* Of the 100 PIs, 28% did not include at least one of the essential information required by the regulations. Pharmacokinetic data, duration of treatment, overdose, and special dosage information were frequently missing. Nine types of clinical information in PIs matched with reference sources resulted in 900 cross-matches. Among the cross-matches, 80 (8.9%) partial compatibilities and 8 (0.9%) total incompatibilities were encountered. Nearly half (48%) of the PIs had at least one incompatibility. *Conclusion:* Some PIs lacked important medicines information and were incompatible with known references. PIs need to be carefully prepared by medicine manufacturers and meticulously reviewed by regulatory authorities for accuracy and completeness.

Keywords

product information leaflet, package insert, medicines information, quality: medication safety, health care professionals

Background

The product information leaflet (PI), also known as package insert, is a document that contains information about a particular medicine and is developed and included within the medicine pack by the manufacturer. It is meant to provide technical information to health care professionals who are involved in prescribing, dispensing, or administering medicines. Therefore, information included in the insert needs to be comprehensive and complete, accurate, and up-to-date. Regulatory authorities of most countries consider it mandatory to evaluate the quality of the PI before registering the medicine in the respective country.

Written sources of medicines information for patients include medicine labels, auxiliary labels, and patient information leaflets. The PI aimed at health care professionals is different from the patient information leaflet that is meant for patients. The types of information included, depth of details, language, presentation of information, and aims of the two differ significantly. However, it has been reported that patients even use the PI for their information needs whenever accessible.[1] Perhaps this may be the reason why most studies related to quality of medicine information have focused on the patient. Many published studies have looked at the completeness, readability, and accuracy of medicine information from the patient's perspective as patients may be harmed if they are unable to read or misunderstand information.[2] Surprisingly, there are not many studies that have focused on the completeness and accuracy of medicine information provided by medicine manufacturers to health care professionals.

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Health care professionals frequently refer the product information leaflet to retrieve information on pharmacokinetics, dosing regimen, safety data, and storage requirements of medicines. With the advent of numerous types of dosage forms and drug delivery systems, information on medicines needs to be checked frequently, even for commonly used ones. Miscommunication of medicines information to the health care professional is detrimental as they are the educators of patients. Inadequate or inaccurate information in product information leaflets can mislead prescribers when prescribing, pharmacists when assessing appropriateness of medicines during dispensing and counseling of patients, and nurses when administering medicines. Besides, PIs are produced by the manufacturer, and there should be an assurance that information is unbiased and evidence based. Although the suitability and quality of PIs are checked at the point of registration by most regulatory authorities, there is no guarantee that the approved PI is enclosed in medicine packs that are available for sale. The dearth of studies that ensure the quality of the medicine information available for health care professionals is an important limitation we observed in the current scientific literature.

The current study was aimed at addressing such limitations and exploring the hypothesis that PIs of medicine packs available in the market may lack in quality even after initial regulatory scrutiny. We looked at two important aspects of quality, the availability of vital medicine information in PIs of medicine packs available in the market and the compatibility of such information with common reference sources.

Methods

An observational, descriptive, cross sectional audit was conducted using PIs found inside medicine packages. The PIs were obtained from a selected state hospital, state-owned community pharmacy, and a private community pharmacy, with the assistance of pharmacists working in study settings mentioned. A pool of 125 PIs was selected. Samples of 100 PIs each were picked from the pool by a simple random sampling method for the assessment of accuracy and availability of essential medicines information. Statistical calculations with a 10% margin of error and 95% confidence level revealed that a sample size of 97 PIs was adequate for each study.

The availability of essential information in PIs was checked against a reference checklist in 100 PIs, selected as specified above. The checklist was developed by a senior pharmacologist and a senior pharmacist mainly based on the regulatory requirements of Sri Lanka (Regulations of the Cosmetic Devices and Drugs Act. No. 27 of 1980, 1984: CDDA)[3]; "Guidance for Useful Consumer Medication Information" of the FDA, USA; and "DISCERN" developed by the British National Library[4] and the University of Oxford in 1997.[4] The researcher checked the availability of information in PIs against the checklist developed.

Nine types of clinical information—namely, indication(s), contraindication(s), precaution(s), adverse effect(s), drug interaction(s), average dose, dosage regimen, duration of treatment, and dosing interval—in 100 PIs were matched with the reference sources British National Formulary (BNF-70)[5] and Australian Medicines Handbook (AMH-11)[6] to assess the level of compatibility, resulting in 900 cross matches. PIs were categorized using an in-house classification system as *compatible* if all facts stated under each clinical information type were mentioned in at least one of the reference sources; *partially compatible* if only some facts mentioned under each clinical information type were mentioned in at least one of the reference sources; *totally incompatible* if none of the facts stated under each clinical information type were mentioned in both references sources; and *not applicable* if the particular clinical information was not present in the PI. The researcher checked the accuracy of each type of clinical information against BNF first, and cross-checked with the AMH when mismatches were observed. All cross matches by the researcher were endorsed by a senior pharmacologist and a senior pharmacist.

This article does not contain any studies with human or animal subjects performed by any of the authors.

Results

A sample of 100 PIs each were assessed separately for availability of essential information and compatibility of such information with common reference sources. There was a 75% overlap among the two samples of PIs selected from the common pool.

Availability of Essential Information

The sample of PIs (N=100) used to assess the availability of essential medicine information included medicines from all classes of the Anatomical Therapeutic Chemical (ATC) Classification (Table 1), and comprised 61 enteral, 32 parenteral, 4 topical, and 3 other (common PIs for medicines available as oral and injectable forms) dosage forms.

We found that 28% of the PIs did not include at least one of the essential information specified by the Sri Lankan CDDA regulations (Table 2). Pharmacokinetic data, duration of treatment, overdose, and dosage information in special situations were types of information that were frequently missing in PIs. Other important information not included in the CDDA regulations were also lacking in PIs. Only 30% indicated the route of administration, 24% specified what to do when an adverse reaction occurred, 32% specified the maximum dose of the medicine, and 50% provided definite information on precautions in pregnancy and lactation. Of the PIs assessed, 93% failed to indicate the sources/references of the information provided, 87% did not specify additional sources of information, and 79% did not indicate the date of publication.

Compatibility of Clinical Information With Reference Sources

The sample of PIs (N = 100) used to assess compatibility of clinical information against reference sources were related to

Table 1. Anatomical Therapeutic Chemical (ATC) Classification of Medicines Related to Product Information Leaflets (PIs) / Package Inserts Included in the Study.

ATC Classification	Frequency of PIs Studied Regarding	
	Compatibility With References	Availability of Information
Cardiovascular system	20	14
Alimentary tract and metabolism	17	16
Nervous system	12	14
Anti-infectives for systemic use	15	15
Respiratory system	8	9
Systemic hormonal preparations excluding sex hormones and insulins	4	7
Blood and blood forming organs	4	6
Genito-urinary system and sex hormones	4	4
Dermatological	3	3
Anti-parasitic products, insecticides, and repellents	2	2
Sensory organs	1	1
Antineoplastic and immune-modulating agents	1	1
Musculoskeletal system	7	7
Various	2	1
Total	100	100

Table 2. Some Essential Information Missing in Product Information Leaflets (PIs) / Package Inserts.

Type of Essential Information*	Frequency of PIs With Missing Information (N = 900)*
Indications	1
Relevant pharmacokinetic data	31
Mechanism of action/pharmacological action	27
Dose interval	7
Warnings/ precautions	35
Drug interactions	20
Contraindications	4
Adverse effects	2
Average duration of treatment	61
Average dose and dose range	5
Dosage in special situations (eg, pregnancy, breastfeeding)	40
References sources of information provided	93
Details of additional sources of support	87
Date of publication	79

*According to the reference list developed using Regulations of the Cosmetics, Devices and Drugs Act No 27 of 1981, "Guidance for Useful Consumer Medication Information" of the FDA, USA; and "DISCERN," developed by the British National Library and the University of Oxford in 1997.

14 medicine classes of the ATC Classification (Table 1) and included 77 enteral, 20 parenteral, and 10 topical dosage forms. The PIs originated from 18 different countries and 49% were from India. Among 900 cross matches, 80 (8.9%) *partial compatibilities* and 8 (0.9%) *total incompatibilities* were encountered (Table 3). Frequencies of incompatibilities related to each type of clinical information are shown in Table 3. Forty-eight percent of PIs had at least one incompatibility. The highest number of incompatibilities was 4 per PI. Most incompatibilities were related to drug interactions. Some examples of items in PIs that mismatched with reference sources are shown in Table 4.

Discussion

A preliminary audit using 100 PIs indicated that some important information was missing. Pharmacokinetic data, duration of treatment, overdose, and dosage information in special situations of medicines, which comprise essential information needed for therapeutic decision making were frequently missing in PIs. Some supplementary information important to determine the validity of information in PIs, such as references and date of publication, were also missing in most. There were instances where information stated in PIs did not completely match with references sources. Such incompatibilities were numerous.

Missing clinical information in PIs could impact in different ways. Information related to pharmacokinetics and pharmacodynamics, drug interactions, precautions, and average duration of treatment are important to make correct treatment decisions and to assess appropriateness of medicines used. Primary and secondary sources of information used for the preparation of PIs and the date of last update are important to assess the validity and reliability of information provided. Unavailability of such information for health care professionals could lead to medication errors or even adverse drug reactions. Unavailability of the average duration of medicine use could lead to misuse of some medicines. Absence of information related to special groups of patients, such as pregnant women or breast-feeding mothers, children, and the elderly, could lead to unsafe or off-label use of medicines and inaccurate dosage regimens. Even the maximum daily dose is important together with the average dose and dosing interval to avoid overdosing of medicines. It must be borne in mind that various brands of a particular medicine may be dissimilar to its originator, clinically and pharmaceutically. Hence, clinical information about known medicines should not be assumed and applied in general by health care professionals. It is important that each medicine pack contains a PI with comprehensive information about the respective medicine and not expect health care professionals to make assumptions.

The nature of incompatibilities between PIs and reference sources varied. We encountered possible typing errors such as "hypertensive" instead of "hypersensitivity," which is a serious miss by the manufacturers that could lead to patient harm. There was also information conflicting with reference sources such as mismatching doses, mismatching duration of treatment, mismatching of precautions and contraindications. It was

Table 3. Compatibility of Clinical Information in Product Information Leaflets (PIs) / Package Inserts Against Reference Sources.

Type of Clinical Information	Frequency of Cross Matches in PIs in Comparison to BNF and AMH (N = 900)*			
	Compatible	Partially Compatible	Totally Incompatible	Not Applicable
Indications	94	4	0	2
Contraindications	68	16	1	15
Precautions	75	8	2	15
Adverse effects	80	12	0	8
Drug interactions	52	21	1	26
Average dose	72	4	2	22
Dose regimen for adults and children	58	9	1	32
Dosing interval	67	5	1	27
Average duration of treatment	9	1	0	90
Total	575	80	8	237

*Nine types of clinical information compared with BNF and/or AMH in 100 product information leaflets; BNF, British National Formulary; AMH, Australian Medicines Handbook.

Table 4. Some Examples of Incompatibilities of Medicines Information Between Product Information Leaflets (PI) / Package Inserts and Reference Sources.

Type of Clinical Information	Medicine Name	Example for Nature of Incompatibility
Indications	Clonazepam	Indications specified in PI are bipolar affective disorder, resistant depression, and chloroform movement, which are not found in reference sources
Contraindications	Oestradiol	PI states contraindicated in severe triglyceridemia, but only cautioned or not mentioned in reference sources
	Enalapril	PI indicates "contra indicated in patients who are *hypertensive* to this products"
	Levothyroxine	PI states contraindicated for "acute myocardial infarction, uncorrected adrenal insufficiency," but only cautioned in reference sources
Precautions	Isosorbide mono nitrate (ISMN)	PI indicates to use with caution in severe hypotension and volume-depleted patients, but contraindicated in reference sources
	Telmisartan	PI indicates to use with caution in biliary obstruction, but contraindicated in reference sources
Adverse effects	Telmisartan	PI indicates hypertension as a side effect, but listed as an indication in reference sources
	Metformin	PI indicates, constipation, dyspepsia/heartburn, flatulence, dizziness, headache, and upper respiratory infection as side effects, but these are not stated in reference sources
Drug interactions	Allopurinol	PI indicates drug interaction with sulphonylureas, but this interaction is not stated in both reference sources
Average dose	Metoprolol	PI states 100-200 mg once-daily doses for angina and cardiac arrhythmias, but reference sources recommend lower strengths in divided doses.
	Esomeprazole	PI states 40 mg b.d. for 7 d for eradication of *Helicobacter pylori*, but reference sources recommend 20 mg b.d. for 7 d
Dose regimen for adults and children	Mefenamic acid	PI indicates doses for age 6 months onwards, but reference sources either does not recommend doses for children below 12 years or recommends doses contrary to that of the PI
Dosing interval	Duloxetine	PI indicates twice-daily doses, but reference sources recommend once-daily doses
	Carvedilol	PI indicates an initial dose of 6.25 mg twice a day, but reference sources recommend a dose of 12.5 mg once daily
Average duration of treatment	Acyclovir	PI indicates duration of treatment for genital herpes as 10 d, but references sources indicate 5-7 d

evident that precautions and contraindications were mixed up frequently, a potential cause for confusion among health care professionals. Some information available in PIs such as drug interactions and precautions was more than that available in reference sources. Being extra cautious about medications may be safer for the patient, but on the other hand, it could also unnecessarily limit therapeutic options for the prescriber. There were PIs that indicated medicines for diseases not indicated in reference sources, which was unacceptable.

This preliminary study indicated that information in PIs that are aimed at health care professionals may be inadequate and may not be completely accurate. This could mislead health care professionals and may affect medication safety among patients. Therefore, we recommend that a minimum set of required

information, most often specified by the respective regulatory authorities of a country, should be made mandatory in PIs included in medicine packs. The information should not be limited only to clinical and pharmaceutical information and should include reference sources with date of publication to enable assessment of validity of information. The target audience of PIs, the health care professional, should be clearly visible so patients would not confuse PIs with patient information leaflet (PILs). Accuracy of information, and the validity of reference sources used by PIs, need to be checked periodically and not only at the time of product registration. It will also be useful for regulatory authorities to have a standard format or template to which manufacturers could adhere to when preparing PIs, which will greatly help to improve uniformity of PIs.

Although we have not looked into the reasons for missing information in PIs, the reasons could be numerous. It could be that evaluation of PIs are not given due priority at the regulatory level or a systematic process of checking for important information is lacking at this stage. It could also mean that medicine manufacturers do not use the same PI submitted for regulatory purposes when marketing their products, or do not inform the regulatory authority of any changes made to PIs subsequently.

Of note, there are also studies that have checked the availability and accuracy of medicine information in commonly used reference sources compared to manufacturer's package insert. A collaborative assessment among 11 pharmaceutical companies to check misinformation in commonly used Online Drug Information Compendia (ODIC) highlights that there may be misinformation in ODIC and alerts consumers and health care professionals to use more than one reference source in their reviews. This is another aspect to be kept in mind when providing accurate and up-to-date medicines information.

We believe that this study is a timely one as it addresses a vital issue related to medication safety. However, some limitations need to be acknowledged to ensure an unbiased perspective to the reader. Firstly the pool of PIs was selected according to convenience and then a simple random sampling method was used to select 100 PIs for analysis from the pool. There is a chance that important medicine types may have been missed, and hence the outcome of this study may not be generalized. We had to strictly adhere to definitions when checking the compatibility of information against reference sources to ensure a systematic process. Some mismatches against reference sources may even contribute to improve patient safety but were still categorized as an incompatibility. Only two widely used reference publications were used to ensure practicality but PIs may have been prepared using other references sources which were not considered. Most PIs did not indicate the reference sources used for preparation and therefore it was impossible to cross check for accuracy.

Conclusions

Information provided in PIs was incomprehensive and not completely compatible with common references. This is not acceptable as PIs are meant to provide information for health care professionals, and any deviation or missing information could result in patient harm. Manufacturers of medicines need to consider this task seriously and ensure that complete, accurate, and evidence-based information is provided in the respective PIs. Regulatory authorities need to urgently and continuously review PIs prepared by medicine manufacturers.

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