Clinical information in drug package inserts in India

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ABSTRACT

Background: It is widely recognized that accurate and reliable product information is essential for the safe and effective use of medications. Pharmaceutical companies are the primary source of most drug information, including package inserts. Package inserts are printed leaflets accompanying marketed drug products and contain information approved by the regulatory agencies. Studies on package inserts in India, in 1996, had shown that crucial information was often missing and they lacked uniformity. Aim: To assess the presentation and completeness of clinically important information provided in the currently available package inserts in India.

Materials and Methods: Package inserts accompanying allopathic drug products marketed by pharmaceutical companies in India were collected. These package inserts were analyzed for the content of clinically important information in various sections.

Statistical Analysis: The results were expressed as absolute numbers and percentages.

Results: Preliminary analyses revealed that most package inserts did contain information under headings, such as, therapeutic indications, contraindications, undesirable effects, etc., listed in the Drugs and Cosmetics Rules 1945. The findings indicated considerable improvement in package inserts since 1996. However, on critical evaluation it was revealed that clinically important information was not well presented and was often incomplete. Information with regard to pediatric and geriatric use was present in only 44% and 13% of the package inserts, respectively. Only five of the inserts had information on the most frequent adverse drug reactions associated with the drug. Also, information on interactions and overdosage was often missing.

Conclusion: Although the package inserts appear to have improved over the past decade there is still a definite need to further refine the clinical information contained, to minimize the risks to patients. This could be brought about by self-regulation on the part of the industry as well as by updating the relevant guidelines in line with those of developed countries.

KEY WORDS: Drug-information, India, package inserts
lists the headings according to which information should be provided in the package inserts.[9] The headings are grouped under two broad sections, with ‘Section 6.2’ listing the headings [Table 1] of immediate importance to the clinical use of the drug, such as, therapeutic indications, posology and method of administration, contraindications, special warnings and precautions, drug interactions, pregnancy and lactation, effects on ability to drive and use machines, undesirable effects, and overdosage.[3] ‘Section 6.3’ lists the headings for ‘pharmaceutical information’ such as, list of excipients, incompatibilities, shelf life, precautions for storage, nature and specification of container, and instruction for use and handling. In fact, the headings mentioned in Section 6.2 of Schedule D are exactly identical to those in the ‘clinical particulars’ section in the European SPC. Although the intended users of package inserts is not explicitly mentioned in the Drugs and Cosmetics Rules, it appears to be directed to the healthcare professionals, and the text in ‘Schedule Y’ of the rules does refer to package inserts as prescribing information.[9]

In India, healthcare professionals depend on a variety of sources, including textbooks and compendiums, for information on drugs.[3] Prescribers are also likely to depend on product information provided by pharmaceutical companies, something not unusual even in developed countries.[6] However, product information provided by pharmaceutical companies in India has been determined to be far from adequate and not conforming with the WHO recommendations.[7,8] Package inserts by virtue of being amenable to strict regulations and being readily available with the drug product can serve as reliable and accurate sources of drug information.[9] Hence, a decision was taken to conduct a study, to evaluate the presentation and completeness of clinical information on package inserts of drug products marketed by pharmaceutical companies in India.

Materials and Methods

Leaflets accompanying allopathic drug products marketed by pharmaceutical companies in India were provided by three pharmacies on request. The pharmacies were located in the proximity of a 1400-bedded, state-run, tertiary care, general hospital in Pune, India. The package inserts were collected over a two-week period in January 2008, and the pharmacies were asked to collect package inserts from drug products that had been dispensed recently. Patient Information Leaflets were identified from the patient-directed language used in the leaflets and were excluded from the study. Duplicates (same drug, formulation, and company) were also identified and excluded. The remaining package inserts were included in the study and analyzed for the presentation and completeness of clinical information. The clinical information included in the package inserts was analyzed according to the headings mentioned in ‘Section 6.2’ of Schedule D of Drugs and Cosmetics Rules, 1945.[13] The package inserts were checked for the presence of each heading mentioned in Section 6.2, followed by scrutiny of the information included under the heading. If a heading was not present in a package insert, the entire insert was checked for the presence or absence of information relevant to the concerned heading. All package inserts were expected to contain information pertaining to the headings listed in the Drugs and Cosmetic Rules, or at least a disclaimer statement regarding the lack of such information. If the information was present under the relevant heading or elsewhere in the package insert it was scored as one, otherwise a score of zero was assigned. After each of the selected package inserts had been scored, the total scores for each heading were calculated by totaling the scores from individual package inserts. The total scores were expressed as absolute numbers and percentages. Information related to pharmacological and pharmaceutical properties of the drugs were also analyzed, but only clinically important findings have been commented upon in the results below.

Table 1: Comparison of contents in the clinical information sections of the package inserts collected for this study with findings from a study by Lal and Sethi (1996)[8]

<table>
<thead>
<tr>
<th>Headings in clinical information section</th>
<th>Present study (n = 80)</th>
<th>Lal and Sethi, 1996 (n = 316)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Therapeutic indications</td>
<td>100.0 (80)</td>
<td>98.4 (311)</td>
</tr>
<tr>
<td>Posology and method of administration</td>
<td>100.0 (80)</td>
<td>100.0 (316)</td>
</tr>
<tr>
<td>Contraindications</td>
<td>97.5 (79)</td>
<td>90.2 (285)</td>
</tr>
<tr>
<td>Special warning and precautions</td>
<td>95.0 (76)</td>
<td>87.0 (275)</td>
</tr>
<tr>
<td>Drug interactions</td>
<td>76.3 (61)</td>
<td>42.4 (134)</td>
</tr>
<tr>
<td>Pregnancy and lactation</td>
<td>86.3 (69)</td>
<td>NR*</td>
</tr>
<tr>
<td>Effects on ability to drive and use machines</td>
<td>16.3 (13)</td>
<td>NR*</td>
</tr>
<tr>
<td>Undesirable effects</td>
<td>96.3 (77)</td>
<td>89.2 (282)</td>
</tr>
<tr>
<td>Overdosage</td>
<td>68.8 (55)</td>
<td>39.2 (124)</td>
</tr>
</tbody>
</table>

Results

Three pharmacies provided 92 leaflets during the study period. Of these, seven duplicates and five patient information leaflets (labeled as such) were excluded from further analysis. The 80 leaflets studied included 38 oral, 36 injectable, and six topical preparations marketed by 35 different pharmaceutical companies in India. The data regarding the presence of important sections described in the leaflets is provided in Table 1. In general, the presentation of information was not uniform and it was difficult to locate and retrieve information easily due to lack of a common layout and headings. Indications for use and contraindications were mentioned most consistently in the package inserts studied. Although, warnings and precautions were included in a majority of the inserts, they frequently lacked information regarding pediatric and geriatric use which were mentioned in only 35 (43.8%) and 10 (12.5%) inserts, respectively. Information about use in special conditions (liver, renal, cardiac, and other relevant conditions) was included in 31 (38.8%) inserts. The drug dose to be administered was not mentioned in three package inserts, including those of rosiglitazone and noradrenaline inserts, whereas, the dosing interval was missing from six leaflets, such as, those of methylprednisolone tablets and ampicillin-sulbactam injection.

[Downloaded from http://www.jgmonline.com on Saturday, July 18, 2009]
Information on adverse drug reactions (ADRs) in the undesirable effects section was only summarily described in most leaflets, and one leaflet merely mentioned that the particular drug was well tolerated and ADRs related to the drug were mild, transient, and rare. None of the leaflets highlighted the serious ADRs associated with the products, which included drugs with abortifacient activity, hypoglycemic effect, chemotherapeutic agents, and drugs commonly associated with hypersensitivity. Only five inserts (6.3%) mentioned the most frequent ADRs observed with the use of the concerned drug. Categorization of ADRs according to organ systems and frequency, which could greatly assist in locating relevant clinical information, was often lacking. Twelve leaflets (15.0%) included information on clinical trial reports of ADRs.

In the studied leaflets, mention of drug interactions was brief and in most instances was limited to drug–drug interactions. Up to seven (8.8%) leaflets did mention drug-food, drug-herb, and drug-lifestyle interactions. Information on drug overdosage was included in 55 (68.8%) leaflets, but information on clinical manifestations and treatment of overdose lacked much detail.

The pharmacological and pharmaceutical property sections also had several deficiencies. Surprisingly, six leaflets did not even mention the international nonproprietary (generic) name of the drug on the package insert. Pharmacological data was present in most leaflets, but specific information regarding the mechanism of action was seen only in 51 (63.8%) leaflets. Pharmacokinetic information regarding the drug was present in 56 (70.0%) leaflets. Information on excipients was included in 55 (43.8%) leaflets only. Description of the product that could be of assistance for rapid identification in drug poisoning and avoiding counterfeits was included in 18 (22.5%) leaflets. Also, the date on which the information in the leaflet was last updated was mentioned in only six (7.5%) labels, which could raise doubts about the recentness of the information.

**Discussion**

This study indicates that the information relevant for the safe and effective use of medications was not uniformly mentioned in the package inserts analyzed. Information on overdosage, drug-interactions, and pregnancy and lactation were most frequently missing in the studied package inserts. It was found that the package inserts seldom, if ever, categorized the ADRs as suggested in the US FDA and EMEA guidelines. Even though most package inserts in this study contained information related to undesirable effects, considerable improvement is still required in this section as well. None of the inserts highlighted the serious adverse events, including ones that could be life-threatening or fatal. Providing such information could be useful, as a study from southern India has shown that more than 56% of hospital admissions, due to adverse drug events, occurred in people aged over sixty years. Also, excipients, which have often been implicated in drug reactions, were mentioned in less than half of the inserts.

When compared with the findings from the study by Lal and Sethi in 1996 [Table 1], there has been an overall improvement in the percentage of inserts containing information under the headings mentioned in Table 1. However, there is still a need to further refine the contents of the circulated package inserts, to make them more complete, reliable, and up-to-date. A limitation of this study could be that only 80 package inserts were analyzed. It may be noted that this study has focused in greater detail on information relevant to clinical use of medications. Another limitation was the difficulty in finding a gold standard to compare the accuracy of the information present in the Indian package inserts. This was due to the fact that information included in package inserts and corresponding documents in other countries could differ significantly in format and content due to variations in the related guidelines and legislations. Also with countries and regions having their own drug safety databases, local labels are likely to include information from these, further adding to the heterogeneity.

Keeping in view the safety of patients using drug products, pharmaceutical companies and regulators have the responsibility of ensuring that accurate and up-to-date product information is provided, and compliance is ensured. Self-regulation by pharmaceutical companies could be part of the solution, but there is definitely a need to update the Indian guidelines for package inserts in line with those from FDA and EMEA. Improvements such as adoption of a uniform format and implementation of guidelines regarding inclusion of relevant information, could greatly enhance the quality and clarity, and appeal to the end users. However, it has also been demonstrated that prescribing information available to healthcare professionals can often be out-of-date, thus calling for regular monitoring to ensure implementation of the guidelines. This is of great importance in India, in view of more than 17,000 pharmaceutical companies manufacturing in excess of 40,000 drug products. Voluntary action by pharmaceutical companies would be very helpful, however, there is an immediate necessity to update our relevant regulations to ensure that risks to the patients are minimized. Finally, the importance of accurate and complete drug product information cannot be overstated, as pharmaceutical products are only as safe as the information that accompanies them.

**References**


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