Original Article

Difference in described indications of medicines among drug information sources in India: An issue urgently to be addressed

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Abstract

Background: Drug information can be obtained from various sources such as National Formularies, drug package inserts (PI), other sources such as Monthly Index of Medical Specialities (MIMS), Current Index of Medical Specialities, and the information available with the regulators. Any variation in the information available in different sources can promote irrational drug use. In this study, we assessed this variation in a sample of commonly used drugs. **Materials and Methods:** Fifty commonly used drugs were analyzed for any variation (both quantitative and qualitative) in information on indications as mentioned in commonly used drug information sources such as Central Drugs and Standards Control Organization (CDSCO) website, National Formulary of India (NFI), MIMS, and PI of medicines. **Results:** We observed a variation in average number of indications per drugs given in CDSCO (2.2 ± 0.25), NFI (3.51 ± 0.42), MIMS (2.98 ± 0.29), and PI (3.18 ± 3.52). The CDSCO and NFI did not contain information about indication for 10 and 17 drugs, respectively, while MIMS and PI contained information about all the selected drugs. A subset analysis was done for 24 such drugs which were mentioned in all the four sources and it was found that NFI had listed the maximum number of indications per drug (3.79 ± 0.53), followed by PI (3.08 ± 0.44), MIMS (3.04 ± 0.51), and CDSCO website (2.66 ± 0.37) and this difference was found to be statistically significant ($P = 0.02$). We also observed some gross qualitative variation regarding drug information given in different sources. **Conclusion:** Variation exists in the quantity and quality of information available on indications about drugs available in various sources. Necessary steps need to be taken to harmonize drug information available across various sources so as to provide reliable and uniform drug information thereby promoting rational drug use.

Key words: Drug information, irrational drug use, off-label

INTRODUCTION

Irrational and inappropriate use of drugs can lead to suboptimal clinical benefit and possible adverse drug reactions (ADRs).[1] Availability of clinically relevant, contemporary, and unbiased drug information goes a long way in promoting rational use of drugs. There are various sources of information which are utilized by treating physicians for accessing relevant drug information such as their indications, ADRs, contraindications, and special precautions. Drug information is usually sourced from National Formularies (e.g. National Formulary of India (NFI), British National Formulary), package inserts (PIs) of drugs, drug compendia such as Monthly Index of Medical Specialities (MIMS), Current Index of Medical Specialities

Access this article online	
Quick Response Code:	Website: www.jnsbm.org
	DOI: 10.4103/0976-9668.175098

How to cite this article: Singh H, Mohan P, Kumar R, Gupta YK. Difference in described indications of medicines among drug information sources in India: An issue urgently to be addressed. J Nat Sc Biol Med 2016;7:93-7.

(CIMS), and medical textbooks.[2,3] The drug information available in various sources should be uniform, reliable, and conforming to the regulatory label of the drug. Every drug is approved for a specific indication(s) by drug regulator of the country, and these indication(s) is/are known as approved indication(s) of the drug.[4,5] If the drug is used for any indication other than the approved indication, it is known as off-label use of the drug. Approved indications of all the approved drugs are available with Central Drugs and Standards Control Organization (CDSCO), which is the national drug regulator in India. It has been observed that there is variation in the quantity and quality of information mentioned in different drug information sources and a single credible benchmark is lacking. Such variation not only deprives the medical fraternity from accessing reliable drug information but can also promote off-label and irrational drug use leading to increased incidence of adverse reactions and possible treatment failure.[5,6] We planned the present study to assess this variation in a sample of randomly selected drugs with respect to their indications given in various sources of drug information.

MATERIALS AND METHODS

We identified 50 commonly used drugs belonging to different groups (e.g. antimicrobials, antihypertensives, analgesics, antiulcer and antiemetics, anticancers, antidiabetics, and antiobesity drugs and also lifestyle drugs such as sildenafil) used in various specialty and superspecialty centers of our hospital. These drugs were chosen on the basis of prescription pattern in the hospital. Two senior residents (D.M. Clinical Pharmacology students) and one PhD student collected and analyzed the PIs of the selected drugs. These drugs were then analyzed for any variations in the information on a number of indications as mentioned in commonly used drug information sources (CDSCO web site, NFI, MIMS, and PIs). The following parameters were assessed.

1. The number of drugs out of the selected 50, whose indication information was missing in different sources.
2. Total number of indications given in different sources, in respect of these 50 drugs.
3. Average number of indications per drug mentioned in different sources.

   After doing the above assessments, we did a subset analysis in respect of:
   a. Only those drugs whose indications were given in CDSCO website list.
   b. In the next step, we compared only those drugs whose indications were mentioned in all the four sources.
4. We also looked upon gross qualitative differences existing across various sources of drug information used in this study.

Statistical analysis

The data were represented as mean ± standard error of mean and median (range). To find the difference between different sources, data were statistically analyzed by applying Friedman Test using Graph Pad Instat (trial version) software.

RESULTS

PIs of all the 50 selected drugs were collected, and they had information about indications which was included in the analysis for comparison. Only MIMS contained information about all the 50 drugs. CDSO and NFI had information about 40 and 33 drugs, respectively. The number of indications per drug was variable in all these four sources. The details of this information are given in Table 1.

A subset analysis was done in respect of only those 40 drugs which were available in CDSCO. NFI was excluded from this analysis as this source had information of only about 24 of these 40 drugs. Hence, this analysis included only three sources (CDSCO, MIMS, and PI). In respect of these 40 drugs, the PI had listed maximum number of indications (2.95 indications/drug), followed by MIMS (2.70 indications/drug) and CDSCO website (2.20 indications/drug). We found that the difference in a number of indications given in these three sources was not statistically significant ($P = 0.07$) [Table 2].

To include NFI as well, a subset analysis was done in respect of those 24 drugs information about which were available in all the four sources including NFI. We found

Table 1: Indication information about the selected drugs

Sources of information	*n*	Total number of indication	Mean ± SEM	Median (range)
CDSCO	40	88	2.2±0.25	2 (1-9)
MIMS	50	149	2.98±0.29	2 (1-12)
PI	50	159	3.18±0.31	2.5 (1-10)
NFI	33	116	3.51±0.42	3 (3-13)

n: Number of drugs about which information is available, SEM: Standard error of mean, CDSCO: Central Drugs and Standards Control Organization, MIMS: Monthly Index of Medical Specialities, PI: Package inserts, NFI: National Formulary of India

Table 2: Indication information available in CDSO, MIMS, and PI

Sources of information (*n* = 40)	Mean ± SEM	Median (range)	*P*
CDSCO	2.2±0.25	2 (1-9)	0.075
MIMS	2.72±0.33	2 (1-12)	
PI	2.95±0.32	2 (1-9)	

n: Number of drugs about which information is available, SEM: Standard error of mean, CDSCO: Central Drugs and Standards Control Organization, MIMS: Monthly Index of Medical Specialities, PI: Package inserts

that NFI had listed maximum number of indications (3.79 indications/drug), followed by PI (3.08 indications/drug), MIMS (3.04 indications/drug), and CDSCO website (2.66 indications/drug). This difference in the number of indications was statistically significant ($P = 0.02$) [Table 3].

Qualitative differences

After the quantitative comparison, we identified any gross qualitative mismatch in information across these four sources. Following gross discrepancies are observed:

1. Of the 40 drugs mentioned in CDSCO, only broad single indication is mentioned in respect of some drugs (e.g. amphotericin B-febrile neutropenia in cancer patients; sodium valproate: All forms of epilepsy; torsemide: Diuretic; fluoxetine: For treatment of depression). It is apparent that such abridged information only reflects the broad use of the drug without providing more specific and relevant information to the prescribing physicians.
2. Labetalol is one of the preferred drugs for treatment of pregnancy induced hypertension, and its oral administration is considered as safe and effective as methyldopa.[7,8] However, as per the CDSCO website, it is indicated for the treatment of all forms of hypertension except hypertension of pregnancy, whereas MIMS and PI mentioned hypertension in pregnancy as one of the indications of labetalol.
3. The CDSCO site mentions the treatment of depression as the only indication for fluoxetine, whereas MIMS and PI mention other indications such as obsessive compulsive disorder, bulimia nervosa also. Surprisingly, NFI lists out the maximum indications for fluoxetine which includes premenstrual disorder, anorexia nervosa, and Parkinson's disease as well over and above the indications given in other three sources.
4. In respect of tablet levofloxacin, CDSCO mention prostatitis as the only indication, whereas MIMS and PI includes more indications.
5. For tablet topiramate, the CDSCO site mentions it only as an antiepileptic, whereas other sources go on to describe the type of epileptic disorders for which it is indicated. In addition, PI mentions prophylaxis of migraine as one of its indication.
6. Besides above variations, some minor typographical errors were also noticed in information provided in CDSCO, e.g., gabapentin being indicated for naturopathic pain instead of neuropathic pain; febuxostat for treatment of chronic hyperuricemia in conditions where urate depression has already occurred instead of urate deposition; sildenafil for pulmonary osterial hypertension and not for pulmonary arterial hypertension.

Table 3: Indication information available in all four sources

Sources of information (n = 24)	Mean ± SEM	Median (range)	P
CDSCO	2.66±0.37	2 (1-9)	0.020
NFI	3.79±0.53	3 (1-13)	
MIMS	3.04±0.51	2 (1-12)	
PI	3.08±0.44	2 (1-9)	

n: Number of drugs about which information is available, SEM: Standard error of mean, CDSCO: Central Drugs and Standards Control Organization, MIMS: Monthly Index of Medical Specialities, PI: Package inserts, NFI: National Formulary of India

DISCUSSION

In India, Drugs Controller General of India is the drug regulatory authority who is responsible for granting approval and marketing permission of drugs in our country. The drugs are approved by drug regulator of any country for specific indications in specified dosage, which is known as the labeling information of that particular drug. However, the actual use of the drug in clinical practice may vary and may not be according to its labeling information at times. Treating physicians can and do use drugs for any indication based on his/her clinical judgment. For example, metformin is used for the treatment of polycystic ovarian disease which is not its approved indication. Such a use of an approved drug is known as off-label use. Off-label use of a drug is not illegal, however, it may be irrational or unscientific.[9]

In order to promote the rational and scientific use of drugs, it is important that relevant information about any drug, namely its indications, contraindications, and dosage are readily available to the prescribing physicians. Some common sources which are relied upon by the prescribing physicians to access drug information are NFI, PI, commercially published drug compendia such as MIMS and CIMS.[2,3] The information available in such sources should confirm with the labeling information approved by the drug regulator of that country so that there is uniformity in decision making irrespective of the source(s) of information.

We undertook this study to assess the quantity and quality of drug information available in various sources and compared it with the labeling information of the drug as provided in the CDSCO website, which is the regulatory benchmark. The information about indications was taken as the sole benchmark of overall drug information, and various sources were compared on the basis of this parameter. It was observed that no information about indications of 10 out of the selected 50 drugs was available on the CDSCO website. Of these 10 drugs, 8 (tablet metformin, tablet acetazolamide, tablet verapamil, tablet carbamazepine, tablet spironolactone, tablet nitrofurantoin,

tablet methotrexate, and injection isoprenaline) drugs were not even mentioned and the rest 2 (tablet propranolol and tablet prazosin) were enumerated without any mention of indications. This can be explained on the basis of the fact that CDSCO website only contains information from 1971 onward, and all these missing drugs are fairly old.

NFI, on the other hand, did not contain information about 17 drugs. NFI is mandated to include all the drugs in National List of Essential Medicines and some other commonly used drugs.[10] The most of the missing drugs (such as risedronate, erythropoietin, and faropenem) are used only in specialized centers and hence shall not be a part of NFI. However, the indication information about some commonly used drugs such as prazosin, levofloxacin, and chlorthalidone was also missing in NFI.

MIMS is a commercially available drug information compendium and was found to contain more number of indications as compared to the regulatory benchmark. Since this source is commonly utilized for seeking drug information, such a discrepancy may encourage off-label, and sometimes irrational, use of drugs.

PIs were also found to contain maximum indications over and above the ones mentioned in regulator's website. In our country, PIs are to be provided to the regulator at the time of registration. However, providing and publishing PIs along with drug packages in neither regulated nor mandatory.[11] In fact, all the pharmaceutical companies do not provide PIs. However, when available, listing any indication in PI which is not in consonance with the regulator's website may again lead to off-label and possible irrational drug use.[12-14]

On the basis of aforementioned, it can be safely inferred that the CDSCO website does not contain information about some commonly used drugs even while these drugs are marketed in India. These 10 drugs are part of 50 commonly prescribed drugs as identified for this study. If all the drugs marketed in India are checked, this number may increase. Such a deficiency has the portent to compromise the robustness of regulatory benchmark and may lead to confusion regarding the appropriate use of drugs.

This study highlights the discrepancies in drug information available in various sources by taking a representative sample of commonly used drugs. To the best of our knowledge, this study, though parsimonious in design, is the first such attempt to address this issue.

These 50 drugs were identified on the basis of the prescription pattern in our hospital which is a tertiary care center. One limitation of this study, is that, this prescription pattern may vary from one hospital to other, and a more broad based selection criteria for identifying drugs may be desirable.

CONCLUSION

Variation exists in the quantity and quality of information on indications about drugs available in various sources. PI and MIMS provide information on indications about maximum number of drugs. However, this information does not conform to regulatory benchmark all the time. Information about a number of drugs was not available in CDSCO website and NFI. CDSCO website is the regulatory benchmark and requires updating so as to provide a sound and reliable reference regarding drug information for all the stakeholders. Further studies involving large sample of drugs and more variables (such as side effect profile, dosage information, information on drug interactions, and special precautions and contraindications) are required to further elucidate the issue of variation in drug information.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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