One hundred and twenty-two new and generic drugs were approved by the FDA in October 2007. The number of drugs entering the market is growing at an alarming rate. In short there is an information explosion. Thus it is almost impossible for a busy medical professional to study and compile the most current and detailed information. During their years of formal training, medical students and residents are exposed to intensive teaching experiences designed specifically to produce clinicians whose skills reflect current best knowledge and practice. But once in practice, they are essentially on their own and face the serious challenge of keeping their knowledge, skills, and performance up-to-date, in the midst of an increasingly hectic professional life.

Sources of Drug Information

The availability of different types of sources of information helps to answer drug-related questions. The main source of information is the published literature which is of different categories, viz. Primary, Secondary and Tertiary. Primary literature is classified as original publications and consists of research studies, case reports, editorials, and letters to the editor. Most primary literature contains a detailed description of the study design, methodology, and scientific results. The reader needs to critique and analyze the study in order to develop a conclusion. Examples of primary literature resources include articles and studies presented in peer-reviewed journals like New England Journal of Medicine, Journal of the American Medical Association, Journal of Postgraduate Medicine, Lancet, British Medical Journal, etc. Secondary literature is compiled by indexing and abstracting services that can be used to systematically locate various types of published literature. Different formats of secondary literature are available in the form of various databases like Medline, Embase, PubMed, National Library of Medicine Gateway, International Pharmacy Abstracts, Current Contents, and Toxline. The information presented in tertiary literature is core knowledge established via primary literature or accepted as standard of practice within the medical community. The tertiary reference may consist of textbooks on various drugs or disease topics (e.g. Harrison’s Principles of Internal Medicine), compendia (a vast array of information about many drugs such as the Physician’s Desk Reference).

Another, but important and significant source of drug information is the promotional literature generated by the pharmaceutical companies. The information is in the form of verbal presentations by medical representatives in the physicians’ clinics, advertising in the journals, direct mailings, organizing CMEs etc. Amongst these strategies verbal presentations by the medical representative is an important source of information as it is readily available and many a times it is the only source on which physicians depend for updating their knowledge.
Shetty, et al.: Promotional literature

Need for Appraisal

Total spending on pharmaceutical promotion grew from $11.4 billion in 1996 to $29.9 billion in 2005. Promotion to physicians continues to be the dominant marketing strategy, but some of the top-selling drugs are promoted by advertising also. The evidence shows that physician prescribing is influenced by pharmaceutical advertisements. The information provided by pharmaceutical companies is concerned more for promotion of their product rather than education. Physicians in training may be particularly susceptible to marketing strategies from representatives. Eleven percent of the verbal statements about drugs made by pharmaceutical representatives to physicians have been found to be inaccurate. More importantly, only one out of four physicians was aware that the information provided was incorrect. Further, a majority of journal advertisements have been found to be based on studies of poor methodological quality. This inaccurate and incomplete information is usually made palatable when given along with gifts ranging from trinkets such as pens and notepads all the way to tickets to attend continuing education conferences in plush vacation spots. Though the objective of the promotional literature is to promote a product, an active approach by doctors can transform it into a useful and accurate source of information. Also, most of the busy practicing physicians feel that promotional literature is a source of education.

Do the present day physicians have sufficient training to deal with medical representatives? In India, there are no courses to train the medical faculty to interact with medical representatives. The only knowledge that is imparted to the second-year MBBS students in the form of a single practical class, when there is no active interaction with the medical representative. In a study conducted by McKinney et al., only 10% of internal medicine faculty and residents felt they had had enough training for professional interviews with sales representatives. Guidelines, codes and regulations for printed and broadcast material exist only in some countries like the UK, Canada and Australia. However, such regulations do not exist in developing countries like India. This further strengthens the need for critical appraisal of promotional literature.

How to Appraise?

General assessment: Be aware of the mental game

Pharmaceutical companies supply the promotional material in the form of flip-charts, brochures and leaflets. Whatever may be the medium, the material is attractive and catches the eye due to its designs, colors and images. Advertising uses images and/or words that appeal to the desires of prescribers such as competence, self-esteem, certainty, gratitude, simplicity or intellectual stimulation. It creates “mental links” between the drug, the indication and the image and associated positive attributes or benefits. This mental link establishes itself in the prescriber’s mind bypassing his critical appraisal defenses. The impact of this influence is further intensified by repetition. Repeated exposures can build small effects which create a long-term impact on the mind of the prescriber. When a patient presents with a particular disease condition, the prescriber will think of the most powerfully promoted drug first. However, in these promotional literatures, key issues like adverse reactions, contraindications, special warnings and precautions may be entirely omitted or presented in very fine print. Hence, the prescriber should look beyond these distractions for complete information of the drug.

What to Look for?

The most important information to be sought from the promotional material includes the following points:

The disease: The drug should be indicated for the conditions for which it is promoted as described by the existing guidelines. The disease under consideration should also be commonly encountered in the respective clinician’s practice.

The need: Does the need for the promoted drug really exist? The physician should consider the problems with the existing recommended therapy and whether the new drug can overcome the problems.

The patient: The patients in whom the drug was tested should resemble the general population. If the patient profile in whom the new drug was tested is substantially different e.g. in age, disease type and severity, then the results cannot be extrapolated to the general population.

The comparator: Careful attention should be paid to the drug with which the new drug is compared. The dose of the comparator should also be same as the dose at which it is prescribed. Using a lower dose of the comparator would produce results in favor of the newer drug.

What was the Outcome (Efficacy)?

The outcome of interest on the promotional material can be classified as disease-oriented or patient-oriented. Disease-oriented outcomes show the results in terms of biological parameters, e.g. BP. This change may not translate into an actual benefit to the patient. This outcome may be interesting, but changing the practice solely on its basis is not appropriate and can be dangerous. The patient-oriented outcome is the one which evaluates actual benefits to the patient in terms of mortality, better quality of life and decreased cost.

No. Of subjects and Statistics: Conducting a study with few patients can jeopardize the results of the study. Hence the study should have enrolled an adequate number of patients to detect a statistically significant difference.

The physician should be equipped with knowledge of the commonly applied statistics. Finding of a statistical significance in the form of p<0.05 may not always mean a clinically relevant significance as it indicates that the difference obtained was a true difference and not obtained by chance. However, it does not provide any information regarding the magnitude of the effect.
The outcome can be presented in terms of risk reduction (absolute/relative), odds ratio, number needed to treat.

Relative risk reduction (RRR) is a method commonly employed to express results. It is the percent reduction in events in the treated group compared to the control group event rate. The RRR is not a good way to compare outcomes. It amplifies small differences and makes insignificant findings appear significant, and it doesn’t reflect the baseline risk of the outcome event. A better statistic is the Absolute Risk Reduction (ARR), which is the difference in the outcome event rate between the control group and the experimental treated group. The ARR does not amplify small differences but shows the true difference between the experimental and control interventions. For example, if the outcome event rates in treatment groups A (old drug) and B (new drug) are 50% and 80% respectively, the RRR will be (80-50)/50 x 100 = 60%. This may be interpreted as treatment B is 60% more effective than control, which is incorrect. Let us look at the ARR, which is outcome rate with B (80%) minus outcome rate with A (50%) = 30%. It can be accurately stated that Treatment B is 30% more effective than the control drug A. Inverse of the ARR gives the Number needed to treat (NNT) i.e. how many patients must be treated with the new treatment for one patient to benefit more than if the patient had been treated with the standard treatment. The NNT is a simple statistic that could be easily interpreted by the physicians as well as patients. The NNT provides the likelihood that the test or treatment will benefit an individual patient. It also provides an impression of the size of treatment effect, such as an odds ratio. Point estimates of effect like odds ratio can often be misleading unless accompanied by a measure of precision, such as confidence intervals. Many claims about new drugs are based on trials having surrogate end points, which are variables that measure rare or distant outcomes of a new drug but are not a measure of direct clinical benefit. They are commonly used in clinical trials because the sample size, duration of the trial and consecutively the cost of conduction of the trial are reduced. Some studies may present their data based on surrogate endpoints to show the superiority of the new drug if the primary objectives of the study are not fulfilled. Physicians should also be aware of the fact that graphical displays of the outcomes in promotional literature often fail to convey the complexity of the data and may distort the findings in favor of the product.

Compliance of the new drug: It indicates if the new drug affects the compliance of the patient. It can be estimated by comparing the spectrum of side-effects of the new drug with the standard drug. It can also be seen by looking at the dropout rates of the trials of the drug. It will also be affected by the type of formulation and frequency of administration.

Cost (Price): Cost of the new treatment is an important consideration for starting the treatment. As new drugs usually have high cost of treatment, it would be inappropriate to prescribe costlier drugs, especially when cheaper and effective alternatives exist. Cost becomes an important consideration for treatment, particularly in a country like ours. Apart from the actual cost of the drug, it also includes the cost to travel to a physician for additional visits for dose titration and for conduction of any test to monitor the effects of treatment. For a drug with a low therapeutic index, cost of Therapeutic Drug Monitoring (TDM) will be added to the cost of a drug.

Supporting scientific evidence: An important aspect to be considered in evaluating promotional literature. Systematic reviews of randomized controlled trials are the strongest level of evidence (i.e., Level I evidence). Other levels of evidence in descending order of strength include non-randomized trials, cohort studies, case-control studies, descriptive or qualitative studies and reports of expert committees [Table 1].

The physicians should insist on sufficient references to substantiate the claims made by the new products. In a study by Lexchin, a majority of journal advertisements have been found to be based on studies of poor methodological quality. For allowing manufacturers to disseminate truthful and non-misleading medical journal articles and medical or scientific reference publications on unapproved uses of approved drugs and approved or cleared medical devices to healthcare professionals and healthcare entities, FDA released a draft guidance for good reprint practices in February this year. When a manufacturer disseminates such medical and scientific information, FDA recommends principles of “Good Reprint Practices” to be followed. The salient features include,

Organizational publications which are peer-reviewed and not funded by the manufacturers of the product in the manuscript.

The manufacturer should not influence directly, or any individual involved in the writing, editing or publishing of the scientific information.
The information in the scientific or medical journal article or reference publications should not be false or misleading and should be derived from adequate and well-controlled clinical investigations.

The information should not pose a significant risk to the public health.

Publications which do not qualify for dissemination to healthcare professionals include letters to editors, abstracts of publications, results of Phase I trials and publications without relevant investigations or data.

Scientific information should not be presented in a form that might bias the judgment of the physician and should be accompanied by the approved labeling of the drug or the device ex. It should be distributed separately from information that is promotional in nature.[17]

Hence, it depends on the skills of the physician to evaluate the quality of the references provided. In general, the references could be evaluated using the above mentioned points. A detailed description of evaluation is beyond the scope of this review. The validity of references could be determined by answering six questions that address the evidence-based principles [Table 2].

A frequently missed, nonetheless very important aspect is to review the disclaimers and acknowledgments of the original study to determine whether a pharmaceutical company funded the study. This is important as published studies that are sponsored by pharmaceutical companies are more likely to have outcomes favoring the sponsor's product.[15]

Improved accessibility and determination of the validity of references in pharmaceutical promotional literature will assist physicians to practice evidence-based medicine.

**Table 1: Levels of evidence[15]**

<table>
<thead>
<tr>
<th>Type of study</th>
<th>Explanation</th>
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<tbody>
<tr>
<td>Systematic review of RCTs with/without meta-analysis</td>
<td>Systematic reviews and meta-analyses are reports of all the results collected after an exhaustive search of the literature; they provide the best evidence to answer a clinical research question. Randomized controlled trials, especially those with double-blind placebo controls, are regarded as the gold standard of clinical research. The most rigorous way of determining whether a cause-effect relation exists between treatment and outcome and for assessing the cost-effectiveness of a treatment.</td>
</tr>
<tr>
<td>RCTs</td>
<td>Main tools for analytical epidemiological research. Findings from observational epidemiological studies are generally less conclusive than those from experimental studies because of the less strict control of extraneous factors.</td>
</tr>
<tr>
<td>Cohort studies and case-control studies</td>
<td>They lack complete ascertainment of cases in any population, definition or enumeration of the population at risk and estimation of the expected number of cases in the absence of exposure.</td>
</tr>
<tr>
<td>Case series and case reports</td>
<td>Expert opinion is the lowest level of evidence and is below experimental evidence.</td>
</tr>
</tbody>
</table>

**Table 2: Criteria for assessing the validity of an article[18,19]**

<table>
<thead>
<tr>
<th>Major criteria</th>
<th>Minor criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was assignment of patients to treatments randomized?</td>
<td>Was the study blinded?</td>
</tr>
<tr>
<td>Were all the patients who entered the study accounted for at the end of the study?</td>
<td>Except from the treatments provided, were the groups comparable in all aspects?</td>
</tr>
<tr>
<td>Were the patients analyzed in the groups to which they were randomized?</td>
<td>Were the study groups similar at the start of the trial?</td>
</tr>
</tbody>
</table>

The information in the scientific or medical journal article or reference publications should not be false or misleading and should be derived from adequate and well-controlled clinical investigations.

The information should not pose a significant risk to the public health.

Publications which do not qualify for dissemination to healthcare professionals include letters to editors, abstracts of publications, results of Phase I trials and publications without relevant investigations or data.

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Improved accessibility and determination of the validity of references in pharmaceutical promotional literature will assist physicians to practice evidence-based medicine.

**Suggestions for the future**

More emphasis should be laid on the evaluation of promotional and other scientific literature while teaching undergraduate students.

Sessions of appraisal of promotional literature should be conducted for interns and resident doctors as they are the ones who usually interact with pharmaceutical representatives.

Initiatives should be taken to form a body for the review of promotional and other scientific material before it reaches the target i.e. doctors or consumers as in direct-to-consumer advertising.

**Conclusions**

The pharmaceutical companies use various strategies to interact with the physicians to promote their product. Although the promotional literature made available by the companies is based on good evidences, this may not be the case always. The evidence supporting the promotional literature may be of variable quality which ushers the need for the physician to appraise the evidence and also ensure its validity. By following the general points of assessing the literature and applying the Safety, Tolerability, Efficacy and Price i.e. STEP criteria,[13] the physicians can quickly judge the quality of the promotional literature. Obtaining and assessing the quality of references is important. The steps of appraisal of the literature provided in this review are an effort to achieve the ultimate goal of medical practice i.e. to ensure the optimum care of the patients.

**References**


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