Published in final edited form as:

J Thromb Haemost. 2008 October ; 6(10): 1680–1684. doi:10.1111/j.1538-7836.2008.03083.x.

Direct-to-consumer advertising for bleeding disorders: a content analysis and expert evaluation of advertising claims

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Abstract

OBJECTIVE—In the United States, the Food and Drug Administration (FDA) requires that all direct-to-consumer advertising (DTCA) contain both an accurate statement of a medication's effects ("truth") and an even-handed discussion of its benefits and risks/adverse effects ("fair balance"). DTCA for medications to treat rare diseases such as bleeding disorders is unlikely to be given high priority for FDA review.

METHODS—We reviewed all DTCA for bleeding disorder products appearing in the patient-directed magazine *HemeAware* from January, 2004 to June, 2006. We categorized the information presented in each advertisement as benefit, risk/adverse effect, or neither, and assessed the amount of text and type size devoted to each. We also assessed the readability of each type of text using the Flesch Reading Ease Score (FRES, where a score of ≥ 65 is considered of average readability), and assessed the accuracy of the advertising claims utilizing a panel of five bleeding disorder experts.

RESULTS—A total of 39 unique advertisements for 12 products were found. On average, approximately twice the amount of text was devoted to benefits as compared to risks/adverse effects, and the latter was more difficult to read (FRES of 20.45 for risks/adverse effects versus 32.08 for benefits; difference of 11.56 [95% CI: 4.52, 18.60]). Only about two-thirds of the advertising claims were considered by a majority of the experts to be based on at least low-quality evidence.

CONCLUSION—As measured by our methods, print DTCA for bleeding disorders may not reach the FDA's standards of truth and fair balance.

Keywords

direct-to-consumer advertising; bleeding disorder; hemophilia; health services

Introduction

Direct-to-consumer advertising (DTCA) is a promotional effort by a pharmaceutical company or other provider of medical services to present information about medications or medical services to the public in the lay media.[1] Spending on DTCA has increased dramatically in the past decade, from \$985 million in 1996 to \$4.2 billion in 2005.[2] Health care providers have been shown to have mixed feelings about DTCA. For example, in a

national survey of 643 physicians, 73% felt it helped to educate patients, but 78% felt it encouraged patients to seek unnecessary treatments.[3]

In the United States, all forms of medical marketing are regulated by the Food and Drug Administration (FDA), which requires that advertisements present a “true statement of information in brief summary relating to side effects, contraindications, and effectiveness.” [4] Advertisers are also charged to achieve “fair balance,” an evenhanded discussion of a product’s benefits as well as its risks and side-effects.[5] Although truth and fair balance became the regulatory standards at a time when medical advertisements were primarily directed at physicians, these concepts have been extended to apply to advertisements directed to patients as well.[1]

In recent years, the FDA has received a remarkable quantity of advertising materials for review; for example, in 2004, 15,458 promotional pieces were submitted. [6] Given this volume, it is unlikely that all DTCA is meticulously evaluated; a recent report by the United States Government Accountability Office (GAO) concluded that the FDA only reviews a “small portion” of the direct-to-consumer materials it receives. Agency officials report placing high priority on materials for television broadcast, non-broadcast materials “that have the greatest potential to impact public health,” as well as voluntarily-submitted draft advertisements.[6] The fact that some materials escape regulatory assessment is arguably most worrisome for rare diseases such as bleeding disorders. This is because as these diseases affect only a small portion of the population, related advertisements are unlikely to meet the FDA’s criteria of having a great potential to impact public health. Due to the high cost of replacement clotting factors for even just one patient, however, such advertisements have the potential to be extremely lucrative for the pharmaceutical companies that make them.

We aimed to analyze the content of print advertisements directed at patients and the parents of patients with bleeding disorders. We chose to focus on advertisements for medications for hemophilia and other congenital bleeding disorders because they seemed unlikely to have been prioritized for review by the FDA (as they are non-broadcast and for rare diseases); we reasoned that if these met the FDA’s standards of fair balance and truth, this would bode well for DTCA as a whole. Using a method we devised for a prior content analysis[7], we aimed to quantitatively assess the risk and benefit information presented in the advertisements, and also qualitatively analyze the accuracy of the claims they make.

Methods

We reviewed all DTCA for medications related to bleeding disorders appearing in the patient-directed magazine *HemeAware* from January, 2004 through June, 2006 (a total of 15 issues). Of note, *HemeAware* is currently the only significant source of print DTCA for bleeding disorders; indeed, two prior content analyses reviewing ten popular magazines did not yield even one advertisement for bleeding disorders.[7,8]

Our analytic methods have been described previously.[7] In brief, an advertisement was selected for analysis if it presented a product intended to directly treat a bleeding disorder or to mitigate its effects. First, for each advertisement, three baseline characteristics were catalogued. An advertisement was considered to include *data* if it had graphs, charts, or numbers/percentages of patients experiencing an outcome or side effect, or if the advertisement mentioned findings from clinical trials. The presence of the image of an apparent *patient* and/or *physician* was also recorded.

Next, benefit and risk/adverse effect assignments were made for the advertisement text using two methods. In method one, each sentence of the advertisement’s text was designated as

“benefit,” “risk/adverse effect,” or “neither” according to its specific content as best assessed by two independent judges. For example, if a product was claimed to “induce fewer inhibitory antibodies” we would consider that statement to be a benefit, as the company would be stating that their product beneficially produces a smaller number of antibodies as compared to other products. Had the statement been simply “may induce antibodies” we would consider this to be a risk/side effect statement.

In method two, a less strict schema, each sentence of text was designated as “benefit” or “risk/adverse effect” according to its own content as above or its contribution to other statements about benefits or risk/adverse effects. For example, consider an advertisement that states “Not all bleeding disorders are equal. Some, like Disorder X are more likely to cause serious hemorrhage. Drug Y treats the worst cases of Disorder X.” The final sentence would be considered “benefit” as defined by both methods; the first two sentences would be “neutral” according to method one, but would be considered “benefit” as defined by method two.

Two judges (GA, MS) independently evaluated each advertisement to assign benefit and risk/adverse effect designations. In all cases when the judges did not concur, a third judge (JW) performed an independent assessment; disagreements were resolved by consensus. In a prior study using similar methodology, inter-rater reliability for the two main judges for a sample of 15 advertisements was excellent before resolution by consensus (average kappa = .87).[7]

Text designated as either “benefit” or “risk/adverse effect” was grouped and analyzed. We then assessed the proportion of total text each comprised, the texts’ placement (first and/or final third), and the largest font size devoted to each. Next, we used Microsoft Word 2000 to determine the Flesch reading ease score (FRES) for the two types of text, calculated with the formula $[206.835 - (1.015 \times \text{average sentence length}) - (84.6 \times \text{average syllables per word})]$. [9] Ranging from 0 to 100, a FRES of 65 or higher is considered understandable for the average person.

Finally, we assembled the *verbatim* claims made in 30 of the advertisements (eg, “safe with respect to viral transmission”), attached a copy to each advertisement, and forwarded them to five bleeding disorder experts. We asked the experts to rate the claims’ *evidence basis*, *exclusivity*, and *clinical importance*, the likelihood that they would *communicate* the benefit to a patient, and the claim’s *accuracy and completeness*. (See Figure 1). We asked the experts to consider “high-quality” evidence to have resulted from large randomized clinical trials, and “low-quality” evidence to be more suggestive, resulting from epidemiological studies, case reports, or anecdotal data. The experts, who represented four states, were all board-certified in adult hematology or pediatric hematology/oncology and worked in either federally-funded hemophilia centers (four experts) or a dedicated pediatric hemophilia/hemostasis practice (one expert). Each was compensated \$150 for his or her efforts.

Results

In 15 issues of *HemeAware*, we identified 145 direct-to-consumer advertisements. After eliminating duplicates, there were 39 unique advertisements for 12 products (see Table 1). Seven of these were “reminder” advertisements (made no specific appeal), and thus were excluded from benefit versus risk/side effect analysis.

There was consistently more information presented about benefits than about risks/adverse effects in the advertisements, especially when using the less strict definitions (ratio of benefit to risk/adverse effect information using method one: 1.96; for method two: 2.51). Benefit information was likely to be present in the first third of text; risk/side effect

information in the final third. The advertisements were difficult to read overall; in addition, there was a moderate difference in the readability of benefit and risk/adverse effect information, more pronounced as defined by method two (Table 2). The largest type size devoted to benefit information was, on average, several millimeters larger than the largest type devoted to risk/side effect information, again with a more pronounced effect seen with the less strict definitions (Table 2). Of note, 38% of the advertisements included *data*, 53% included the image of an apparent *patient*, and 0% included the image of an apparent *physician*.

The results of the experts' assessment of the advertising claims are presented in Table 3 and Table 4. About two thirds of the advertising claims were rated as based on at least low-quality evidence by a simple majority of the experts; about one third were rated by a majority of the experts as not evidence based. Of note, no single product had more than two advertising claims fall into this category, which included claims about effectiveness, convenience, safety, packaging, and quality of life. For most claims, a majority of the experts at least somewhat agreed the claim was clinically important and that they would be likely to communicate the benefit to patients. Interestingly, only about one-third (36.6%) of the claims were rated by a majority of the experts as being presented both accurately and completely; a larger number (53.3%) were considered to be presented accurately but incompletely (*i.e.*, contextual information was missing).

Discussion

We found that, as a group, print DTCA for bleeding disorders arguably contains several possible breaches of the FDA's requirement for truth and fair balance. Most notable is the presence of at least twice the amount of benefit information when compared to information about risks/adverse effects. In addition, while all information presented is difficult to read as assessed by a standard measure of readability, benefits are significantly more readable and are presented in much larger text. Moreover, of 30 advertising claims evaluated, only about one third were rated by all five experts to be based on at least low quality evidence.

While our results are in line with prior analyses regarding benefit and risk information presented in general television and internet DTCA [10,11], they stand in contrast to our study of oncology-related print DTCA, where we also found poor readability overall but essentially no *differences* in readability between benefit and risk/adverse effect text.[7] In addition, while our oncology study found the difference in type size between benefit and risk/adverse effect text to be 2.22 mm on average, this difference was almost double in the current study (4.18 mm) using the same methodology. It is possible that these differences reflect a relative lack of scrutiny for print advertisements for rare syndromes by the FDA. Indeed, of the 19 letters issued in 2004 and 2005, only six were for print advertisements, and not one was for DTCA for products used to treat bleeding disorders.[6]

Another explanation for the differences between oncology-related DTCA and DTCA for bleeding disorders may lie in the nature of the products being advertised. Much of oncology DTCA is for supportive treatments such as anti-emetics and hematopoietic growth factors, or for arguably "optional" adjuvant therapies such as hormonal treatments for breast cancer. In contrast, replacement factors for bleeding disorders are not optional; here, the goal of marketing is less to convince patients or their parents to start using products, but more to encourage them to switch from one product to another. This may result in an effort by marketers to emphasize the benefits of replacement factors over their risks, which are known to be minimal with modern production techniques. This can be a tough task, given that these products do not generally demonstrate significant differences in efficacy.

The accuracy of the advertising claims presented in DTCA is difficult to assess, even with extensive review of the medical literature. This is because a claim might be considered inaccurate simply because a supportive published paper is not found, or considered accurate despite the fact that data from the literature is misapplied or taken out of context. We believe that the ideal assessment of such claims is thus made through assessment by expert clinicians familiar with the breadth of published and unpublished data supporting the claims as well as the context in which that data is appropriately applied. While our method admittedly has its drawbacks, that fact that of 30 *verbatim* advertising claims, only about two-thirds were rated by a majority of our experts as being based on low quality evidence or better seems provocative. This is perhaps even more interesting given the fact that the experts did not consider the majority of the claims to be obscure or clinically insignificant.

Our study has limitations. First, we cannot determine ultimate effects: it is possible that the overall poor readability of DTCA for bleeding disorders does not affect consumer or provider behavior at all, or that there are other variables that are more important to the advertisements' comprehensibility. Indeed, readability itself is only one dimension of the presentation of information that may affect comprehension.[12] For example, the type of information itself (benefit versus risk/adverse effect) might influence comprehension, as patients may pay more attention to risks/adverse effects than to benefits.[13] Indeed, fair balance surely takes into account many factors beyond the ones we measured (text size and FRES), and our measurements may not be the ideal ones. Second, our method of assigning benefit and risk/adverse effect status to sections of advertising text is, by its very nature, subjective. Third, our expert assessment was limited in scope, used a small number of experts, and did not make an effort to obtain consensus (eg, with a modified Delphi or RAND/UCLA technique).[14,15] If we had worked with a larger number of experts and focused on achieving consensus, our results may have been markedly different.

A final limitation merits discussion. For scientific and ethical reasons, the FDA criteria for approving products for bleeding disorders often do not necessitate reaching the "high-quality" standard of large randomized clinical trials. This may explain the lack of reported "high quality" evidence ratings on the part of our expert reviewers. Moreover, for those claims that were not supported by high-quality evidence, our methods did not allow the experts to report if this was because there was evidence against the claim, or if there was simply limited or no good evidence for the claim. On the other hand, it may be argued that the presence or absence of high-quality supporting evidence is all that matters: while manufacturers must advertise according to their FDA-approved labeling, we are not sure if patient-directed information should include claims that are not based on high-quality evidence from clinical trials, even when they are accepted by the FDA and therefore likely meet that agency's criteria for "truth."

In summary, as a group, print DTCA for bleeding disorders may breach the FDA's requirements for truth and fair balance as measured by our methods. This conclusion is supported by our finding that only about two-thirds of the advertising claims were assessed to be based on at least low-quality evidence by a majority of bleeding disorder experts, and that, as compared to risks/side effects, substantially more text about benefits was presented in the advertisements in both larger type and in a more readable manner. These characteristics of DTCA for bleeding disorders may reflect the complexity of the type of information being presented; indeed, it may not be possible to make information about replacement factors comprehensible to the untrained consumer or to present the "truth" about the subtleties of such products in an advertisement without the context of a clinical encounter. This second possibility raises the question of whether or not consumers are truly prepared to receive such product or medication information "directly" through advertising; assessing DTCA's readability and the relevance of its information using a panel of patients

with bleeding disorders is a logical next step for further research. Indeed, in a recent Internet survey, 324 respondents were asked about their preferences regarding information on medication websites.[16] Interestingly, 78% said they specifically wanted numerical information about the incidence of side effects, but only 53% also preferred the inclusion of the incidence of side effects with placebos. This lack of desire for a reference group with respect to side effects suggests that many consumers are not adequately prepared to evaluate even the most basic information presented in direct-to-consumer campaigns.

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Product XYZ
Claim: "Safe with respect to viral transmission"

1. Given your knowledge of the medical literature, would you rate the above claim:

- ☐ Based on high-quality evidence
- ☐ Based on low-quality evidence
- ☐ Not evidence-based
- ☐ Do not know the literature well enough to evaluate the claim

2. The benefit described in this claim is:

- ☐ Characteristic only of the advertised product, not the other drugs for the indication
- ☐ Characteristic of all products for the indication, including the advertised product
- ☐ Characteristic of some products for the indication, including the advertised product
- ☐ Not a benefit of the medication

3. The benefit described in this claim is clinically important:

- ☐ Strongly Agree
- ☐ Somewhat Agree
- ☐ Somewhat Disagree
- ☐ Strongly Disagree

4. I would likely communicate the benefit in this claim to my patients, when discussing this drug:

- ☐ Strongly Agree
- ☐ Somewhat Agree
- ☐ Somewhat Disagree
- ☐ Strongly Disagree

5. In my opinion, the advertisement presents the benefits of Product XYZ:

- ☐ Completely and accurately
- ☐ Fairly accurately, but not completely (e.g., unbalanced information is missing)
- ☐ Inaccurately

Figure One.
Questionnaire for Claims Assessment

Table One

Products Advertised in HemAware, January 2004 to June 2006

Brand name	Generic name/contents
Advate	Recombinant Factor VIII, advanced generation
Alphanate	Plasma derived antihemophilic factor with Factor VIII/Von Willebrand Factor
BenefIX	Recombinant Factor IX
Genarc	Recombinant factor VIII
Helixate FS	Factor VIII, recombinant, formulated in sucrose
Humate-P	Plasma derived antihemophilic factor with Factor VIII/Von Willebrand Factor
Kogenate FS	Factor VIII, recombinant, formulated in sucrose
Mix2Vial	Factor reconstitution system
Monarc-M	Factor VIII, plasma derived, monoclonal antibody purified
Mononine	Factor IX, plasma derived, monoclonal antibody purified
NovoSeven	Recombinant Factor VIIa
ReFacto	Recombinant factor VIII, B-domain deleted

Table Two

Characteristics of DTCA for Bleeding Disorders

Characteristic	Benefit Text	Risk/Adverse Effect Text	Difference (95% Confidence Interval)
Text placement in first 3 rd (method 1)	87.5%	18.8%	--
Text placement in final 3 rd (method 1)	40.6%	75.0%	--
Readability (FRES, method 1)	32.08	20.45	11.56 (4.52, 18.60)
Readability (FRES, method 2)	36.73	22.04	14.68 (7.66, 21.71)
Largest Type (method 1)	6.58	2.39	4.18 mm (2.90, 5.45)
Largest Type (method 2)	8.67	2.39	6.28 mm (5.18, 7.38)

Note: for text placement, percentages refer to frequency of unique advertisements with benefit or risk/adverse effect text found in their first or final third of text. For readability, note that a FRES of 65 or greater is considered readable for the average person. Method 1 and method 2 refer to the two ways of defining benefit and risk/adverse effect text.

Table Three

Five Experts' Assessment of Evidence Supporting Claims

	Percent (of 30 claims)
Percent of claims all experts rated "based on high-quality evidence"	0.0%
Percent of claims all experts rated at least "based on low-quality evidence" or better	33.3%
Percent of claims majority of experts rated at least "based on low-quality evidence" or better	66.6%
Percent of claims all experts rated "not evidence based"	3.3%
Percent of claims majority of experts rated "not evidence based"	30.0%

Note "majority" was defined as 3 or more out of 5 experts when all answered; if 1 expert did not feel qualified to answer or left the question unanswered, 3 or more out of 4 was required to reach majority; if 2 experts did not feel qualified to answer or left the question unanswered, 2 or more out of 3 was required to reach "majority."

Table Four

Five Experts' Assessment of Characteristics of Claims

Majority of experts....	Percent of all claims evaluated (30 claims)
...agree claim is characteristic of only advertised product, not any others for indication	23.3%
...at least somewhat agree claim is "clinically important"	93.3%
...at least somewhat agree they would be likely to communicate benefit described in claim	96.6%
...feel claim presents benefit "accurately and completely"	36.6%
...feel claim presents benefit "accurately but not completely" (contextual information is missing)	53.3%

Note "majority" was defined as 3 or more out of 5 experts when all answered; if 1 expert did not feel qualified to answer or left the question unanswered, 3 or more out of 4 was required to reach majority; if 2 experts did not feel qualified to answer or left the question unanswered, 2 or more out of 3 was required to reach "majority."