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Important Drug Safety Information on the Internet

Assessing its Accuracy and Reliability

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Abstract

Background: The Internet is becoming increasingly important as a source of health-related information, but the accuracy and reliability of information presented on the world wide web is debated.

Objective: We aimed to assess whether important, recent drug safety information is accurately reflected on Internet sites.

Methods: We evaluated whether major warnings issued by the US FDA between October 1, 2000 and September 30, 2001 on severe and life-threatening drug toxicity were mentioned 4–16 months later in the top ten web pages identified for these drugs by each of seven different search engines. We examined predictors of precise mention of the FDA warnings using logistic regressions.

Results: Twenty major safety warnings on 21 drugs (including three withdrawals) were eligible for the study. Among 519 different pertinent web pages retrieved (16–32 for each drug), precise mention of the safety issue was made in only 165 (31.8%). Best rates of precise mention were seen in web sites sponsored by attorneys (79.4%), in physician-oriented web pages (65.5%) and for withdrawn drugs (57.9%). In addition to these factors, better coverage of the FDA warnings was independently seen when no other adverse effects from the same organ system was mentioned ($p < 0.001$), while coverage was worse when there was no date on the site and web page ($p = 0.020$), and when the site owner could not be classified or was unknown ($p = 0.014$).

Conclusions: Important safety warnings are inadequately covered in the majority of web pages. This deficiency creates a source of potentially harmful misinformation for health consumers.

Background

The Internet has caused an information revolution of unprecedented magnitude and is increasingly used as a risk management tool by both health professionals and consumers. Seeking valid information on the Internet can be difficult because of the speed and lack of control with which the information is accumulating.[1] Quality criteria commonly agreed upon include currency, reliability, relevance and accuracy.[2] Several studies have tried to assess the impact of web sites on physician and patient behaviour[3] and have shown that the Internet is assuming an increasingly important role in disseminating health information.[4] Drug safety is an important aspect of healthcare. However, it has not been evaluated whether health-related web sites are regularly and accurately updated for newly released guidance on major drug adverse effects.

In order to answer this question, we targeted major drug-related safety warnings issued by the US FDA and assessed whether this information was captured in web pages found when searching the Internet about the drugs involved.

Methods

Criteria for Selection of US FDA Warnings

We searched for pharmaceutical drug products with major safety warnings (withdrawal or life-threatening or serious toxicity) posted in the FDA site (www.fda.gov/medwatch/safety.html) during the period October 1, 2000 to September 30, 2001. Biologics (blood components, fractionated blood products; antitoxins; proteins; manipulated, cultured, or expanded human cells; vaccines; gene transfer products), dietary supplements and medical devices were excluded. We also excluded warnings for mislabelling, withdrawals of specific lots, and referrals to new document supplements (patient's brochures, medical guide, informed consent). Whenever the warning pertained to more than one drug, we considered a separate warning for each drug, unless it pertained to the use of drugs in combination. All warnings were screened for eligibility by two independent investigators who generally agreed on which warnings should be included.

We used each warning to extract information on drug trademark, drug generic name, FDA posting date, safety issue, severity (withdrawal, life-threatening adverse effect warning, serious safety warning) and on whether the specific type of adverse effect was newly discovered or was known in the past but important new attributes of severity, frequency or management were discussed.

Search Strategy for Web Pages

We used the following seven search engines: Google (www.Google.com), Lycos (www.lycos.com), Excite (www.excite.com), Yahoo (www.yahoo.com), HotBot (www.hotbot.com), Infoseek (www.infoseek.com), and Copernic 2000 (www.copernic.com). These search engines represent some of the most common options for Internet surfing by general consumers. Drugs were searched using both trade and generic names, unless the safety warning referred to the substance irrespective of the drug product, in which case the search used only the generic name.

Data Extraction from Web Pages

We performed a pilot investigation for two eligible drugs (nevirapine [Viramune®[1]] and topiramate [Topamax®]) in order to establish the best way possible to manage the huge bulk of information. It was impossible to evaluate all the retrieved web pages, since the number per search engine ranged between 70 and 8650 for Viramune® and 50 and

1 Use of tradenames is for product identification only and does not imply endorsement.

9345 for Topamax®. Therefore we decided to use for analysis only the top ten web pages appearing in the results for every drug and for each search engine. The top ten pages would be most likely to be perused by health consumers. We excluded web pages in languages other than English, those that required subscription to provide information, and those that simply referred to other search engines.

The selected pages were extracted in detail between December 29, 2001 and February 10, 2002. A data extraction form was piloted by four independent investigators on the sites identified for Viramune® and Topamax®. This pilot investigation helped us to amend the form to improve clarity, maximise retrieval of pertinent information and ensure high consensus between the data extractors.

The final form captured general site information, i.e. the web address, search engines yielding the certain site as top ten (if a page was extracted by the same search engine twice we counted it once for this search engine), dates of web page and site update, and site owner or sponsor (classified as government, pharmaceutical company, university or professional organisation, patient organisation, attorneys, unclassifiable [including other site owners less directly involved in the medication market, such as individuals, publication companies and non-pharmaceutical industries], unknown); content (classified as adverse effects [including precautions], indications, chemistry, mechanism of action, interactions, dosing, and cost) and orientation (patient, physician or both); and information on safety. We identified whether there was a precise mention of the adverse effects reported on the FDA warning. Precise mention did not require exact use of the same words, especially in patient-oriented sites, but the nature and the degree of severity had to be presented. If a drug was reported for more than one adverse effect, we evaluated both whether all adverse effects had been mentioned and whether at least one of them had been mentioned. We also recorded the coverage of other adverse effects; of severe and life-threatening adverse effects; and of other adverse effects from the same organ system as the one involved in the FDA warning. We speculated that coverage of a major warning may leave less room for reporting other, more minor, adverse effects, especially from the same organ system. Coverage of minor adverse effects from the same organ system without mention of the major adverse effect may be particularly misleading.

Whenever we got different sub-pages without the home page of the site, we kept each sub-page as a separate item. Whenever we got different sub-pages as well as the home page, we kept each sub-page as a separate item, and we also extracted the sub-page of the home page that provided the most extensive safety information, if this was different from the sub-pages that had been hit directly. Finally, whenever we got only the home page, we kept the sub-page that provided the most extensive safety information, unless there were several sub-pages equally pertaining to safety, in which case we included all of them in the same form.

Analysis

The major outcome was the precise mention of the index side effect pertaining to the posted FDA warning (including all adverse effects in the warning). We evaluated predictors of this outcome using logistic regressions. Both univariate and multivariate models were used. Multivariate models were built with forward selection of variables according to likelihood ratio criteria. Each web page was counted as an observation. In the main analysis, each page was counted once, regardless of the number of top ten hits. Candidate predictors included the time since the posting of the warning by the FDA, the type of the warning (withdrawal vs other), the severity of the index side effect (life-threatening vs other), the type of web page, whether there was any date on the site or page, whether the pertinent ad-

verse effect was completely newly recognised or not, the ownership and orientation of the web page, and the reporting of other safety parameters.

Analyses were conducted in SPSS 10.0 (SPSS, Inc., Chicago, IL). P-values are two-tailed.

Results

We identified 20 eligible FDA major safety warnings (table I). One warning was for two drugs, thus making a total of 21 eligible drugs. With two exceptions, the warning pertained to only one available drug product, while for phenylpropanolamine hydrochloride and miconazole there were several different preparations from different companies. There was a very large variety of adverse effects (table I). Fifteen drugs had warnings about life-threatening adverse events, and six for severe. Three drugs (alosetron [Lotronex®], rapacuronium bromide [Raplon®] and cerivastatin [Baycol®]) were withdrawn. Safety warnings for 11 drugs referred to adverse effects that were already known about but important attributes of severity, frequency or management were newly discovered and warnings for ten drugs referred to completely newly discovered adverse effects.

A total of 519 different eligible web pages were evaluated (16 to 32 for each drug). The majority had one (n = 206 [39.7%]), two (n = 134 [25.8%]), or three (n = 82 [15.8%]) appearances in the top ten hits across search engines, while 97 pages were hit 4–7 times. Total eligible hits were 1217. The 15 drugs with life-threatening adverse effects had 393 pages (75.7%). Seventy-six pages (14.6%) pertained to the three withdrawn drugs. About half of the pages (n = 269 [51.8%]) referred to the ten drugs with completely newly discovered adverse effects. Only 89 pages belonged to daily updated sites (17.1%) and in another 164 (total n = 253, i.e. 48.7%) the web page or site date was later than the date of the FDA warning release. More than one-third (n = 188, 36.2%) of the pages had no date either on the eligible page or on the site. The site owner/sponsor was the pharmaceutical industry in 47 cases (9.1%), the government in 65 (12.5%), a medical association or university in 74 (14.3%), attorney organisations in 34 (6.6%) and patient organisations in 10 (1.9%), while the owner/sponsor could not be classified in these categories in 215 cases (41.4%), and was unknown in 74 (14.3%).

The content of the web pages is summarised in table II. As shown, even though our protocol selected the parts that were most relevant to safety, there was usually some general coverage of indications, even at a higher percentage than any coverage of adverse effects and precautions. Several other parameters were often addressed (table II). Most pages did not specify their orientation, while 129 were oriented towards patients, 77 towards physicians, and ten towards both.

Precise mention of the FDA warning occurred in only 165 web pages (31.8%) accounting for 410 of the 1217 hits (33.7%). A total of 190 pages (36.6%) had a precise mention of either all or at least some of the warning adverse effects. Other adverse effects were mentioned in half of the pages, but numerical frequencies thereof were provided infrequently. One of four pages reported other life-threatening adverse effects and a third mentioned other adverse effects from the same organ system.

In univariate analyses, precise mention of the FDA warning was more common if the drug had been withdrawn, but even then many of the web pages failed (table III). Precise mention was conversely less common if the adverse effect was not life-threatening. As expected, the rate was lower when a sub-page was directly hit, rather than when a safety-oriented selection was made from the home page. Moreover, sites with daily updates had modestly better precise safety coverage and this was true also when any date was mentioned in the web page or site. Site ownership affected the rate of precise mention, with highest rates in attorney sites and

Table I. Eligible major safety warnings posted in the US FDA web site during the period from October 1, 2000 to September 30, 2001

Tradename	Generic name	Date safety warning posted	Safety issue (severity[a])	Old/recent[b]
Serentil®	Mesoridazine besylate	Oct 10, 2000	QT prolongation, 'torsade de pointes', sudden death (life-threatening)	Old
Various	Phenylpropanolamine HCl	Nov 6, 2000	Haemorrhagic stroke especially in women (severe)	Recent
Viramune®	Nevirapine	Nov 9, 2000	Fatal hepatotoxicity (life-threatening)	Old
Xeloda®	Capecitabine	Nov 28, 2000	Overdosing in renal failure (severe)	Recent
Lotronex®	Alosetron HCl	Nov 29, 2000	Serious constipation, ischaemic colitis in female subjects (life-threatening)	Old[c]
Zerit® and Videx®	Stavudine and didanosine	Jan 5, 2001	Fatal lactic acidosis in pregnancy, when combined (life-threatening)	Recent
Exelon®	Rivastigmine tartrate	Jan 31, 2001	Vomiting in reinitiating therapy (severe)	Old
Zyvox®	Linezolid	Mar 2, 2001	Myelosuppression (life-threatening)	Recent
Various vaginal preparations	Miconazole	Mar 5, 2001	Increase of prothrombin time, bruising and bleeding (severe)	Recent
Trisenox®	Arsenic trioxide	Mar 19, 2001	QT prolongation, complete atrioventricular block, 'torsade de pointes', sudden death (life-threatening)	Old
Pepcid®	Famotidine	Mar 23, 2001	Overdosing in renal failure (severe)	Old
Raplon®	Rapacuronium bromide	Mar 29, 2001	Bronchospasm, unexplained fatalities (life-threatening)	Recent[c]
Orlaam®	Levomethadyl acetate HCl	Apr 20, 2001	Arrhythmias, cardiac conduction prolongation, deviations of the abnormal heart rhythm (life-threatening)	Old
Diprivan®	Propofol	Apr 25, 2001	Deaths in intensive care unit in paediatric patients (life-threatening)	Recent
Lamisil®	Terbinafine HCl	May 9, 2001	Liver problems resulting in liver failure and death (life-threatening)	Old
Sporanox®	Itraconazole	May 9, 2001	Congestive heart failure (life-threatening)	Recent
			Liver failure and death (life-threatening)	Old
Cordarone®	Amiodarone HCl	Jun 8, 2001	Fatal or developmental effects on neonates and infants (life-threatening)	Recent
OxyContin®	Oxycodone HCl	Jul 25, 2001	Abuse, misuse, diversion: serious effects, death (life-threatening)	Old
Baycol®	Cerivastatin	Aug 8, 2001	Fatal rhabdomyolysis (life-threatening)	Old[c]
Topamax®	Topiramate	Sep 26, 2001	Ocular syndrome/permanent vision loss, in paediatric populations (severe)	Recent

a Life-threatening adverse effects are those that have already resulted in observed deaths and have the potential for causing death.

b Adverse effect that was known in the past but important attributes of severity, frequency or management were newly discovered (old) or adverse effect that was completely newly discovered (recent).

c Voluntary withdrawal by pharmaceutical corporations and the FDA.

Table II. Content and safety reporting in the 519 eligible web pages

	Number of web pages (%)
Content	
Adverse effects/precautions	375 (72.3)
Indications	414 (79.8)
Chemistry	112 (21.6)
Mechanism of action	167 (32.2)
Interactions	172 (33.1)
Dosing	220 (42.4)
Cost	22 (4.2)
Safety reporting	
Precise mention of US FDA warning	165 (31.8)
Other adverse effects	254 (48.9)
with numerical data	76 (14.6)
Other life-threatening adverse effects	
none	384 (74.0)
one	67 (12.9)
more than one	68 (13.1)
Adverse effects from same organ system	161 (31.0)

lowest rates in sites from patient organisations, unclassifiable owners and unknown owners. Precise mention was more common when the site clearly mentioned that it was oriented towards physicians. However, the overall rates of precise mention in pharmaceutical, governmental, professional, and university sites (the types of sites more likely to be visited by physicians and healthcare providers) were generally not very satisfactory (table III). Sites that reported other adverse effects or other adverse effects from the same organ system were less likely to have precise mention. Precise mention was not influenced by whether the warning pertained to a completely newly discovered or old adverse effect and by whether numerical information was provided or not for other adverse effects (table III). The number of top ten hits was also not a significant predictor (odds ratio 1.08 per hit, $p = 0.17$) and there was no evidence that earlier warnings were likely to have a higher rate of precise mentions (odds ratio 0.999 per month lapsing between the date of warning being issued and the date of the Internet search).

In multivariate modelling (table III), the odds of precise mention decreased significantly when no date was given neither for the site nor for the web page ($p = 0.020$), when the site owner was unclassified ($p = 0.014$), and when a sub-page was directly hit rather than through making a safety-oriented choice from the home page ($p = 0.006$), while the odds of precise mention increased when there was a physician orientation ($p < 0.001$), when the drug was withdrawn ($p < 0.001$), in legal sites ($p < 0.001$), and when no other adverse effects from the same organ system were mentioned ($p < 0.001$).

Discussion

Recent surveys show that 40–54% of patients access medical information via the Internet. This information affects their choice of treatment.[5-9] Nevertheless, some of this information may be inaccurate or outdated.[10] This may be particularly important when it pertains to major drug adverse effects. Misinformed patients may fail to recognise toxicity, or may even not stop taking drugs that have been withdrawn. Our study showed that precise mention of major adverse effects that were covered by FDA warnings occurred in only about one-third of the evaluated web pages in searches conducted between 4 and 16 months after the issuing of these warnings. Our study also identified several parameters that affected the rates of precise mention of FDA warnings.

Accessibility, quality and reliability of health-related web sites has varied across empirical studies,[11,12] but deficiencies are probably common overall.[11] Nevertheless, only a minority of patients expresses uncertainty about the accuracy of medical information on the web.[9]None of the previous empirical studies have focused specifically on safety-related issues. Overt trust in an information source may be dangerous, if the information provided is suboptimal and if it pertains to issues that may even jeopardise the consumer's life and well-being.

Table III. Number of sites providing a precise mention of a US FDA warning about adverse effects according to various parameters

Parameter		Precise mention (%)	Multivariate OR (95% CI)
Drug withdrawal[a]	Yes	44/76 (57.9)	2.98 (1.66–5.34)
	No	121/443 (27.3)	1.00
Severity of adverse effect[a]	Severe	25/126 (19.8)	NS
	Life-threatening	140/393 (35.6)	NS
Type of web page[a]	Direct sub-page	130/445 (29.2)	0.45 (0.25–0.79)
	Selected from home page	35/74 (47.3)	1.00
Site daily updated[b]	Yes	37/89 (41.6)	NS
	No	128/430 (29.8)	NS
Dates mentioned in web page or site[a]	None	43/188 (22.9)	0.56 (0.35–0.91)
	Any	122/331 (36.9)	1.00
Site owner[a]	Attorney	27/34 (79.4)	8.45 (3.19–22.4)
	Government	30/65 (46.2)	1.00
	Pharmaceutical industry	18/47 (38.3)	1.00
	Medical association/university	28/74 (37.8)	1.00
	Unknown	17/74 (23.0)	1.00
	Patient organisation	2/10 (20.0)	1.00
	Unclassifiable	43/215 (20.0)	0.56 (0.35–0.89)
Orientation of web page[a]	Not reported	68/293 (23.2)	1.00
	Patient only	40/129 (31.0)	1.00
	Physician or both	57/87 (65.5)	3.85 (2.30–6.44)
Other adverse effects mentioned in web page[a]	None	111/265 (41.9)	NS
	Any	54/254 (21.3)	NS
Numerical frequencies for adverse effects mentioned in web page	Yes	24/76 (31.6)	NS
	No	141/443 (31.8)	NS
Adverse effects from same organ system mentioned in web page[a]	None	136/358 (38.0)	2.73 (1.64–4.54)
	Any	29/161 (18.0)	1.00
Completely newly discovered adverse effect	Yes	87/269 (32.3)	NS
	No	78/250 (31.2)	NS

a $p < 0.01$ in univariate analysis.

b $0.01 < p < 0.05$ in univariate analysis.

CI = confidence interval; **NS** = not selected (not significant) in the multivariate model; **OR** = odds ratio.

Web pages with unclassifiable site owners were the least likely to mention the FDA warnings. A previous study has found that governmental or professional organisations provide more accurate information.[13] Even apparently credible sites may not necessarily provide high levels of accurate health information.[14] Pages that clearly stated that they are oriented towards physicians had better safety coverage, but it was also not perfect. Pharmaceutical, government, and professional sites are the ones most likely to be visited also by physicians seeking updated safety information. The overall rates of precise safety coverage were not very satisfactory in such sites. Thus not only health consumers, but also health providers may be misled by outdated Internet information. The best coverage across all subgroups was seen in attorney sites, a finding pointing to the prominence of malpractice claims in current healthcare.

Currency of the site is also important to consider. Safety warnings were far less likely to be reported in sites and web pages that provided no dates. While the Internet has offered an excellent tool for updating information in real time, several sites may not be regularly updated and a large proportion may provide no insight on how recently they have been updated. Furthermore, the FDA warnings were less frequently covered, when other adverse effects from the same organ system were mentioned. Apparently the reported severe adverse effects might have overshadowed other toxicity from the same organ system. Finally, as expected, warnings on withdrawn drugs had better coverage.

A limitation of our study is that the surfing behaviour of each Internet user in real life may vary, while in our research setting we selected a structured search strategy following a robust algorithm. Relatively little is known about how consumers might search for health information. One study has shown that Internet users explore only the first few links on general search engines when seeking health information, rarely go to a sub-page or a second link if they do not find the answer, and alteratively refine their search strategy using one search term rather than combinations of words.[15] The average user may not be focusing on safety messages, unless this was the original purpose of the surfing. Overall, it is likely that our results may overestimate the chances that a common user may retrieve and assimilate precise information on the specific adverse effects covered by the FDA warnings.

Our findings should not be interpreted as evidence that the Internet provides less updated and less accurate information on drug safety than other more conventional sources of healthcare information. Although drug safety is theoretically as important as drug efficacy,[16] toxicity issues may still be relatively neglected, even in the best peer-reviewed medical literature[17] and adverse effects may remain unknown until a drug has been on the market for many years.[18] Moreover, it has been shown recently that it is very difficult to obtain additional clarifications on safety data even when the primary investigators of clinical trials are being contacted.[19] If experts and researchers have difficulty obtaining safety information from published studies, the average healthcare consumer may be at a much more difficult position. Given its versatility and speed of updating, if quality can be ensured,[20,21] the web could actually become a prime tool for spreading new important safety information to patients and even to physicians that have not yet been exposed to these data from other sources. The clinical implications may be considerable, since this is critical information that may enhance the quality and appropriateness of healthcare.

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