

White Paper

ADVERSE EVENT REPORTING ON HEALTH WEBSITES – A PILOT STUDY

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Abstract

Reports suggest the growing use of social media for discussing drug related adverse events (AEs). In this paper, we investigate the use of health websites as a source of AEs based on assessment and analysis of data across three drugs.

We also discuss the importance of monitoring AEs cited on the internet and challenges associated with monitoring, assessing and reporting these. We identified 713 AEs from our investigation across a 3 month search period and across 3 products. Of these total AEs, 55 were unlabeled and serious.

We expect that this investigation will serve as an aide to an informed discussion amongst the pharmaceutical companies and the regulators about using the internet, and specifically, using health websites as a valid source of AE reports and an additional avenue to obtain safety information on marketed drugs.

Keywords:

Social Media, Hits, Adverse Events, US FDA

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1. INTRODUCTION

The use of social media and internet is becoming a prominent part of the healthcare delivery system. Health consumers use the internet for a variety of reasons, to share health information, to obtain drug related information and side effects, to form a support group for patients, and as a virtual location to collectively understand treatment options and their availability. [The Pew Foundation' study](#)¹ found that 39% of patients use online support groups to discuss medications or treatments with other patients. The study suggests that this number would only grow in the future.

We conducted a pilot study to understand the use of health websites for discussing AEs experienced by consumers. The approach, objective, process, findings and conclusion of the study are presented in this paper.

2. APPROACH:

The scope of this pilot included a review of health related websites and health message boards. Popular social networking sites such as Twitter, Orkut or Face Book were not included in this study. The primary objective of this pilot study was to determine the extent to which health websites and health boards are used by consumers to share product related AEs. Most pharmaceutical companies have dedicated websites for their drugs, primarily for disseminating information about their proper use, and a few of these websites also provide forums for patients to discuss their use of the drug and their experiences. ['PatientsLikeMe'](#) is an example of a site where consumers share drug related experiences. The results of this study could be used to determine if it would be useful to expand the scope to conduct a broader search across the internet, not limited to health websites.

Atypical antipsychotics are often the subject of discussion related to AEs. Hence this drug class was chosen for this pilot. In order to assess the magnitude of AE discussions on health websites, drugs that are most prescribed or widely used in its class were chosen for the study. Also, the drugs had to be on the market for a sufficient time period for people to start a discussion on it.

In order to eliminate any reporting bias related to a particular product, two atypical antipsychotics were selected (AP1 and AP2) for investigation as part of this pilot study. These are amongst the top 5 most prescribed in the class. In addition, one OTC (over the counter) product, amongst the most widely used drug in its class, was chosen to understand the extent to which OTC products that are known to be 'relatively safe' are discussed on the internet. Since the mid-90s several prescription medicines have been converted to OTC. There is less input from health care professionals into recommendation or ongoing monitoring of use for OTC products and hence limited opportunity for monitoring of safety and ongoing patient follow-up. Hence this class of products merits special attention with respect to spontaneous reporting of AEs, as discussed in the paper on [safety monitoring of OTC medicines in the Drug Safety Journal in 2003](#)². AEs related to all the three products were manually searched on health websites and health boards over a defined period of time.

3. OBJECTIVES OF THE STUDY:

- To evaluate the extent of use of health websites by consumers for discussing drug related AEs
- To assess the utility of monitoring AEs discussed on internet
- To discuss the validity of AEs and the challenges associated with monitoring and reporting AEs discussed on the health websites.

4. PROCESS:

Following the selection of drugs to be studied, a 3-month time frame was determined so as to collect the most recent information available on the websites. Drugs were searched on Google for websites containing product information or AE related discussions. After a search process, a total of 70 websites were identified to be used for the investigation. These websites were chosen on the basis of drug related hits. Most of these were health related websites or had discussion on

health related topics. Search terms used were the terms routinely used for search of scientific literature, for example, drug name and side effect, drug name and toxicity etc. Searches were conducted and adverse events were captured from all drug-related hits. Suspected AEs were coded using MedRA to the LLT level and terms were assessed against product monograph to determine if the AE was labeled or not. CIOMS (Council for International Organizations of Medical Sciences) seriousness criteria were used to assess the events.

The process followed for this pilot study has been depicted in Figure 1.

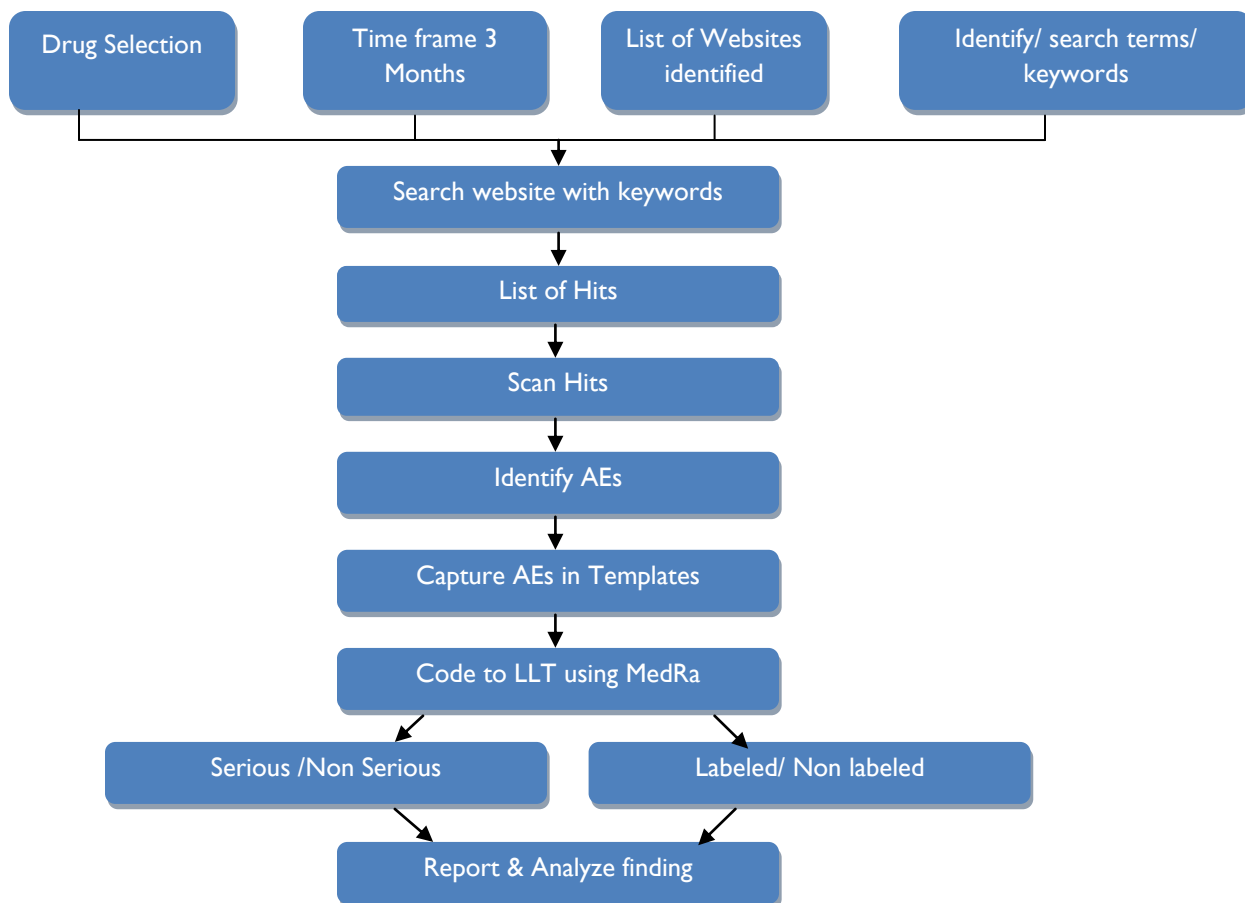


Figure 1: Process flow diagram

A data sheet was designed to capture information on AEs. AEs reported between June and August 2009 were evaluated in this study.

5. FINDINGS

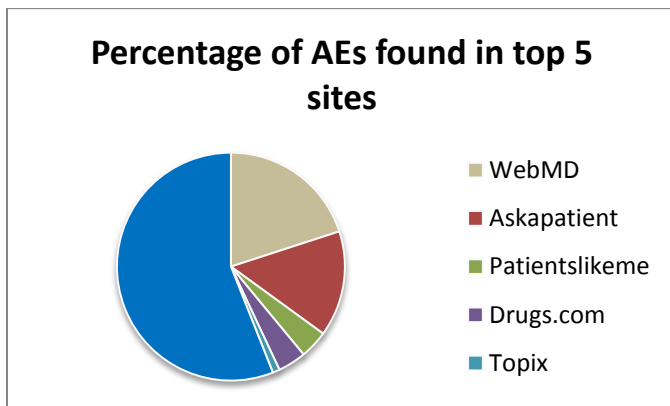
Findings from this pilot study are presented below.

I. Extent of use of health websites for discussing drug related AEs

Study results suggest that a substantial number of health websites are used by consumers for discussing their experiences which are ‘suspected’ to be due to the drug.

The top five common sites across all three products that reported AEs, of the total sites that were searched, are listed in Figure 2.

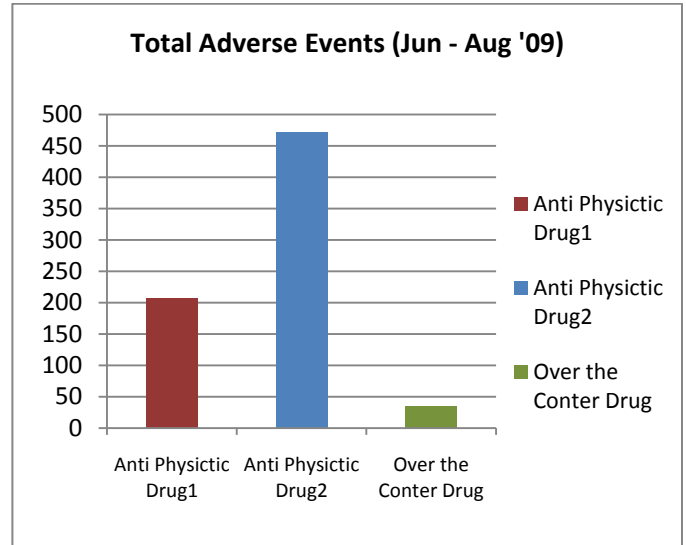
Figure 2: Top 5 common sites that reported AEs across all three products



It was observed that the top 5 sites shown in Figure 2, accounted for 44 percent of the total AEs captured across the three products. For each of the 3 drugs investigated, almost half of the sites surveyed had at least one suspected adverse event. This suggests that a large number health related websites are used for sharing AEs.

During the 3 month period of the pilot-study, over 700 AEs were identified across the 3 drugs. The annualized count would be over 2800 AEs. Figure 3, below, shows the total number of AEs reported between June and August 2009 for the 3 products.

Figure 3: Total number of Adverse Events reported between June – August 2009

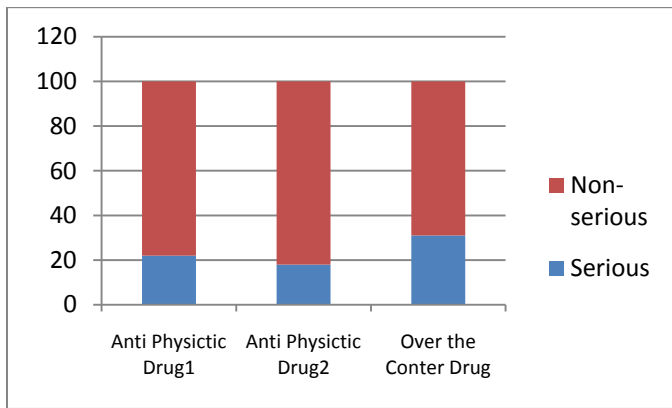


Twice the number of AEs was identified for AP2 (antipsychotic drug 2) when compared to those of AP1 (antipsychotic drug 1). It is difficult to comment on this observation since 3 months is a small period to observe trends or to correlate the occurrence to any incident.

II. Assessment of the Utility of Monitoring Adverse Events Reported On Internet:

Serious and unlabeled AEs found in this study suggest that it would be useful to monitor AEs reported on the internet. Figure 4, below, shows the percentage of serious and non-serious AEs for the three products studied. Seriousness of adverse events was assessed by a medical reviewer using CIOMS seriousness criteria.

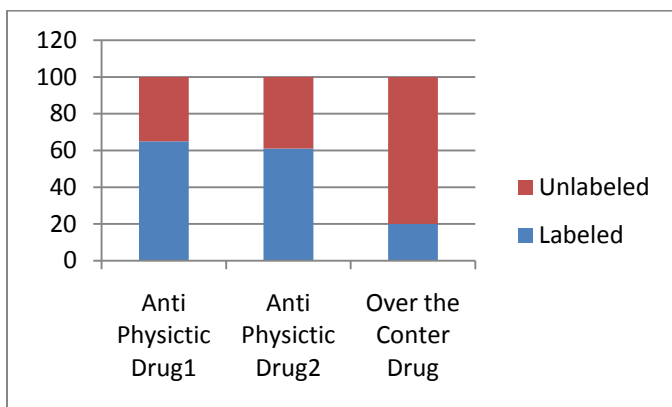
Figure 4: Percentage of Serious and Non-serious Adverse Events for all 3 products



Forty-six out of 207 AEs for AP1 and 86 out of 471 AEs for AP2 were identified as serious. For the OTC product 11 out of 35 AEs were serious. The number of serious AEs is sizable, especially considering that the search was limited to a three month period.

Figure 5, below, shows the percentage of labeled and unlabeled AEs for the three products studied.

Figure 5: Percentage of Labeled and Unlabeled Adverse Events for all 3 products

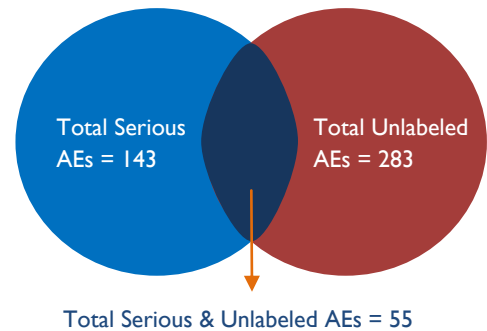


For AP1, 73 out of 207 and for AP2 182 out of 471 AEs were unlabeled. For the OTC product, 28 out of 35 AEs were unlabeled. Again, considering that the period of search was only 3 months, the number of unlabeled events across 3 drugs appears to be high. We note that 80% of events for the OTC product were unlabeled

while less than 40% events were unlabeled for the anti-psychotics. This is in line with our expectations, given that safety monitoring in the post-marketing phase for an OTC product would have been much less than for the antipsychotics. One reason for low reporting of AEs for OTC products could be the absence of two of the three primary reporters, the prescribers and the dispensers. It's also useful to note that less than 30% of the AEs on the OTC product were serious, which is also in line with the expectation that AEs with an OTC product are less likely to be serious.

Figure 6, below shows total number of serious and unlabeled AEs and their intersection.

Figure 6: Intersection between unlabeled and serious AEs across all 3 products



Product wise data of the total number of unlabeled serious, serious and unlabeled AEs are shown in Table 1, below.

Table 1: Number of Unlabeled Serious Adverse Events for all 3 products

Drug	Total Serious	Unlabeled Serious	Total Unlabeled
AP1	46	19	73
AP2	86	32	182
OTC	11	4	28

In this study we observed that within the 3 month period, 26% of AEs for AP1, 18% for AP2 and 14% for the OTC product are unlabeled serious AEs.

FDA's July 2009 draft guidance for industry entitled *Postmarketing Studies and Clinical Trials – Implementation of Section 505(o) of the Federal Food, Drug and Cosmetic Act*³ states that post-marketing studies and clinical trials may be required for any or all the three purposes listed below:

- To assess a known serious risk related to the use of the drug
- To assess signals of serious risk related to the use of the drug
- To identify an unexpected serious risk when available data indicate the potential for a serious risk

Product AE information gathered from the internet could supplement the information already available with the FDA and the pharmaceutical companies about product related risks, even if some AEs discussed on websites may already have been reported to the manufacturers or regulators. This supplemental information can aid in FDA's or the companies' safety evaluation of a drug. This is even more relevant for OTC products, given the low reportability of AEs for these products to the manufacturers or regulators. Data from the Division of Drug Risk Evaluation, Office of Drug Safety, Center for Drug Evaluation and Research for the period 1990-2001, suggests that only 5-10% of the reports per year in AERS⁴ (Adverse Event Reports System) are related to the OTC drugs. Compliance to the regulation for OTC reporting that was released in December 2007 is increasing, but may take some time to reach the levels of prescription products. Moreover, as mentioned before, two of the three primary reports are missing for OTC products. Thus any safety information obtained from the internet would be particularly useful for OTC products.

III. Discussion on the Validity of AEs and the Challenges associated with Monitoring & Reporting AEs discussed on the internet:

According to FDA's March 2001 draft guidance for industry titled *Postmarketing Safety Reporting for Human Drugs and Biological Products Including Vaccine*⁵, following four minimum data elements are required to include in a post marketing individual case safety report:

1. An identifiable patient
2. An identifiable reporter
3. A suspect drug or biological product
4. An adverse experience or fatal outcome suspected to be due to the suspect drug or biological product

Patients or reporters reporting on the internet can typically be identified by the user name or user ID that they have used to post the AEs. The key challenge is to determine what constitutes an identifiable patient or reporter for AEs reported on the internet. There could be two ways to define an identifiable patient or reporter for the events posted on the internet, one is to have the email ID, or address or phone number of the patient or reporter and the other is to consider the user ID or user name as a valid identifier for the patient or reporter.

All the events captured in this study mention the suspect drug and suggest that the event is due to the suspect drug, although the messages do not always contain adequate details to properly establish a causal relationship between the drug and the AE.

FDA also defines '*Spontaneous Report*⁵' in its March 2001 draft guidance. Spontaneous reports are unsolicited communications from individuals (e.g., health care professional, consumer) to applicants that concern adverse experiences. *For spontaneous reports, the applicant should assume that an adverse experience or adverse event was suspected to be due to the suspect drug or biological product (implied causality).*

AEs reported on the internet could be classified as a form of unsolicited communication from the consumer, except that such communication is not addressed to the applicants. However, the causality for such events is to be implicitly assumed. Thus, all AEs captured in this study met 2 of FDA's reporting criteria i.e. suspect drug and adverse event suspected to be due to suspect drug. Only 1 out of the 713 AEs met all 4 reporting criteria. On the other hand, if user ID and user name can suffice the requirement of an identifiable patient and or reporter and since the causality between a drug and AE is implicitly assumed, all 713 AEs captured in this study met all 4 reporting criteria. A fairly large number, 55 of these, were serious and unlabeled.

Verifying if the AEs reported on the internet have also been reported to the regulatory authorities is a challenge.

It is also likely that the same AEs are reported on several sites since a patient or reporter may subscribe to multiple sites and post the same AE on all the sites. In this study, we found one AE which was duplicated on 3 sites. The same user name and AE description was posted on all the 3 sites. Our criteria to sift duplicate AEs from the 'once only' reported AEs was by checking if the same user name or ID has been used again and or if the same description has been posted on other sites. If the findings of this study are representative of what may be generally observed, then we can conclude that duplicity of events may not be of serious concern. However, it is possible that there is some duplication on sites which do not fall in the scope of this study.

Mining and monitoring of AEs reported on the internet is an arduous task based on the efforts undertaken in this pilot study and as has also been presented in the [PharmaMarketing News](#) ⁷ article. Manually searching and extracting the AEs from the hits is time-consuming.

It is difficult to determine the authenticity of the AEs posted on health websites. Medical confirmation of AEs

is generally not available, and there could be several different reasons for posting AEs on the internet.

The challenge for the pharmaceutical industry is lack of clarity about its responsibility to report AEs discussed on websites. This has also been mentioned in [PharmaMarketing News](#) ⁶ article, along with a recommendation that the FDA could take a small step and define the industry's responsibility to report AEs that they come across on websites.

However some pharmaceutical companies are already looking at the social media for adverse event related information. In June 2009, UCB, a Biopharma Company and "PatientsLikeMe", announced a strategic partnership to create an online, open, epilepsy community that captures real-world experiences of people living with epilepsy in the U.S. The FDA had also called for a [public hearing](#) ⁷ in November 2009 on internet adverse event reporting. FDA has solicited public opinion about adverse event reporting on social media.

6. CONCLUSION:

We have some evidence from this study to indicate, based on the number of adverse experiences we found, that health websites constitute an important source of safety information that can supplement safety information obtained through conventional means. We found that forty five percent of the total sites we reviewed had cited AEs. Several of these were serious and unlabeled events. In view of the number of the events observed, it is important to regularly monitor these sites for AEs. Our findings differ from findings reported in other publications. For e.g., the [clickz.com](#) ⁸ article states results from a 2008 study wherein out of 500 randomly selected healthcare messages online, only 4 messages (less than 1%) mentioned an adverse event. The challenges faced in searching the events can be overcome by using a customized tool that would

help search the sites. One tool for monitoring blogs and other social media is mentioned in [PharmaMarketing News Vol. 8, No. 9: October 2009 article is 'Radian 6'](#)⁶. A clear guidance on the scope of a company's responsibility for monitoring and evaluating AEs reported on the internet would be helpful as has also been suggested in the [PharmaMarketing News article](#)⁶.

The US FDA can also help define 'what constitutes a reportable event' on the internet. If the FDA could also provide guidelines to define the scope of the search on internet, the process of reviewing AEs reported on the internet would become less complicated. An article in the [Pharmaceutical Executive, September 2009](#)⁹ indicates that the large pharmaceutical companies are acutely aware of the need to use social sites to interact with consumers in real time, but are looking for some guidelines to structure the 2-way dialog. A similar point is made in [The Upside of the Downturn, September 2009](#)¹⁰.

In conclusion, the findings of our study indicate that health websites are an important channel used by consumers to discuss adverse events. And some of the recent discussion on this topic suggests that if the US FDA issues a clear set of guidelines about using social media for safety monitoring as well as for communication and marketing, pharmaceutical companies would be more open to participate in social media. Since we observed several AEs for the OTC product we included in the study, it may be useful to conduct another focused pilot study for OTC products in order to assess the utility of social media for AE reporting specifically for OTC products. The report from the Center for Drug Evaluation and Research ([AERS](#)⁴) also discusses limitations of spontaneous reports and the need to look at other sources for more drug risk data. Thus looking at social media for more information on AE discussions may be useful for OTC products.

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