

**Adverse Drug Reactions: Problems with Spontaneous Reporting Systems and
Communicating Information to Providers to Improve Reporting Rate Globally**

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Adverse drug reactions – problems with spontaneous reporting systems and communicating information to providers to improve reporting rate globally

Adverse drug events are common occurrences and consequences of adverse drug reactions and/or medication errors. Previous studies have shown that approximately 5-10% of the internal medicine patient admissions were cases of adverse drug reactions. In addition, another 5-10% of all the inpatients were likely and expected to suffer from severe and dangerous adverse drug reactions. Not surprisingly, among the leading causes of death in the Western world are reported to be adverse drug reactions (Pirmohamen et al., 2004). Adverse drug reactions are defined by the World Health Organization as “an effect which is noxious and unintended, and which occurs at doses used in man for prophylaxis, diagnosis and therapy” (Neubert et al., 2004).

The reporting of adverse drug reactions is a worldwide affair and it has been reviewed and studied in many countries. The main goal of pharmacovigilance is early detection of new and/or unusual adverse drug events and minimal patient exposure to such events. Identification of adverse drug events is crucial to health care because their impact results in significant social costs estimated in billions of dollars annually and unnecessary, often fatal, harm to patient (Bates et al., 1997 & Classen et al., 1997).

More recently, many post-marketing and large-scale clinical trial studies have been specifically designed to discover and keep track of new adverse drug reactions. Gibbons et al. (2010) suggest that some, or maybe most of these studies are not exactly the ideal representation of the potential medication users, have short or unreasonable follow up periods, possibly inadequate sample sizes, and unattainable control group (due to necessity of treating a person with a certain condition and inability to have an ill person act as the non- treatment group

participant). They also suggest that it is important and needed to shift from spontaneous ADR reporting to more longitudinal medical claims and medical records. Also, coherence of experimental design strategies, statistical methodologies, and association of different databases (such as ecological methods for rare adverse events, meta-analysis of randomized controlled trials, medical claims data) is the best way to approach successful adverse drug reactions and events reporting (Gibbons et al., 2010).

Considering the potential important effects of adverse drug reactions, many monitoring systems have been developed, a common and popular one being the spontaneous reporting system. Spontaneous reporting systems (SRSs) are resources holding within reports of suspected post-marketed ADEs. SRSs are the mainstay of pharmacovigilance today. The major spontaneous reporting systems include the United States Food and Drug Administration's (FDA), Adverse Event Reporting System (AERS), and the World Health Organization (WHO) Program for International Drug Monitoring (Harpaz et al., 2010).

Traditional methods of detecting adverse drug events in spontaneous reporting system databases relies on manual case reviews by pharmacological/clinical experts. But due to increasing inconvenience and large size of spontaneous reporting system databases, other methods were proposed consisting of quantitative and automated approaches that are referred to as DMAs (data mining algorithms) or signal detection algorithms. These methods are designed to identify statistically significant associations between drugs and adverse effects (AEs). The aforementioned 'signals' are not necessarily true adverse drug effects. They are hypotheses documenting and necessitating further investigation to qualify them as credible adverse drug effects. These allow their evaluators to review enormous numbers of reports and to focus their concern on potentially important safety issues (Harpaz et al., 2010).

In the past few years, many other DMAs have been developed for screening potential ADEs (Hauben et al, 2005). In order to estimate incidence rates, data mining algorithms use reports in the SRS system as a figure for the true population. Most of the DMAs depend on the use of DR (disproportionality measures), like RR (reporting ratio) that quantify the degree of unexpectedness of certain Drug-Adverse Event association. Reporting ratio (RR) is used by both, WHO and FDA in order to monitor safety signals in SRSs (Evans et al., 1997 & Classens et al., 1997).

Databases of spontaneous reporting system contain many thousands of adverse effects and drugs and it is a daunting task to mention all of the possible combinations of adverse drug events for final statistical analysis. In order to avoid data base wide studies, recent work focuses more on demographic groups or only specific drugs of interest. Also, most recent data mining algorithms are specifically designed to select and identify bi-variate associations only, for example, pairs identifying only one drug and one adverse event, while excluding multi-item associations, such as two drugs and one or two adverse events. These multi- item associations have quite useful potential because they can lead to important drug-drug interactions knowledge and findings. They are also the less studied phenomena and the studies that considered and studied multi-item with adverse drug event associations (such as drug-drug interactions) did so only post careful selection of a small set of drugs (van Puijenbroek et al., 1999).

The association rule process [or mining, as Harpaz et al., (2010) call it] is a greatly understood process for discovering important relationships between variables within large databases. An association rule of adverse drug events detection (where $A \rightarrow B$, and A and B are not related) A is a set of drugs and B is a set of adverse events. A true example of this phenomenon is A indicating Aspirin and Warfarin, and B ndicating bleeding. The association

rule strength is evaluated by the support and the confidence of the rule, where the confidence shows how often items in B appear in recordings that contain A, and the support of an set is the record number containing A, not B (Harpaz et al., 2010).

Association rule mining allows for a natural setting of adverse drug effect analyzing and their detection. Recently it has been approved to many biomedical surveillance areas of problems, such as association rule mining to hospital infection control (Brosette, 1998). Chen et al. also have applied the association rule to a database comprised of a hospital admissions dataset and a pharmaceutical dataset for identifying patient groups, which are more prone to adverse effects to medications. Lastly, Rouane et al. has also applied the association rule mining to identify adverse drug events to anti-human immunodeficiency virus drugs. Overall, the association rule mining proves to be quite useful in both, hospital settings and in a broad range of research settings.

However, while the association rule mining has great use and potential, Harpaz et al. (2010), identified some key issues that must be addressed when this association rule mining is applied at work. Initially, they report that the interesting multi-item associations search space is vary large, and that discovery of these associations in large databases is quite expensive. For example, the number of possible associations made of 3 drugs and 2 adverse events needing to be examined is about $10,000^5 = 10^{20}$. For this large number, then, incidence rates must be calculated and examined. As it can be seen and imagined, this is way too large of a setting to be convenient and easy to use. Also, some of the incidents discovered could easily be only happening by chance and have nothing to do with the actual reality association. Some of these may also be happening due to confounding factors, as suggested by the authors. Harpaz et al., (2010) also took into account both of these potential issues in the association rule mining and

have addressed them in this study. They suggest using association rule mining as a crucial and very promising first step in a process that is multi-step, where these steps have strategic statistical analysis and pharmacological/ clinical judgment of many expert personnel. As mentioned before, the multi-item associations space in large databases (adverse event reporting systems databases) is very large and quite difficult to pursue due to the number of possible rules to search. In order to take care of this potential issue, the researchers of this study used an efficient algorithm and employed additional criteria in order to reduce the space available to search, which were specific to the application. These additional criteria ensure high confidence and high support. In order to specifically identify association rule in large databases, the researchers used the 'Apriori algorithm' that made it possible to take care of cases such as the following: when a certain combination of drugs and adverse events was uncommon, then any other larger combination that builds upon the smaller infrequent one, will also be infrequent and, therefore, will not need to be considered, thus ignored. While it is quantitatively unclear of how much this algorithm decreases the search system by, the scale of computational gain that was reached by these aforementioned optimizations was more than several thousand folds (Harpaz et al., 2010). This study clearly examined the feasibility of a known mining of data method when combined with multi-item adverse drug event detection in SRS reporting systems, demonstrating its value as a part of a greater operational set-up that includes expert knowledge associated with other statistical methods. Their experimental method was set up in a database manner to AERS of FDAs with some small restrictions. Their results show that multi- item adverse drug events are present, however they could be extracted from the AERS using their methodology of minimal restrictions (Harpaz et al., 2010).

The notion of ‘surprise reactions’ observed in the course of evaluating data mining algorithms has been considered and studied by other scientists as well. These adverse reactions are less clinically relevant or dramatic, less characteristic of drug effects broadly speaking and may have subtle pharmacological explanations. The concept of ‘unexpectedness’ was studied to determine the aforementioned associations, and it was found that the identification of these ‘surprise reactions’ could serve as a very important display for data mining algorithms. It is important to note that analysts of DMAs must not be too quick to dismiss drug-event associations that have potential to occur, as being possible non-drug factors. Pause and thought should be incorporated during this review and even the pharmacology of the drug should be contemplated before dismissal (Hauben et al., 2007).

Adverse drug events are reported throughout the world and depending on the country, different systems are used. Spontaneous reporting of adverse drug reactions (ADRs) is one of the different methods of pharmacovigilance. For example, in United Kingdom this is done through Yellow Card Scheme, which was established in 1964 as a consequence of a thalidomide tragic incident (Metter, 2004). While the Yellow Card System is quite efficient and useful, it has been found to be a bit tricky to understand how to use. Anderson et al. (2011) successfully derived the three methods (telephone, paper and internet) of reporting to the Yellow Card System and were able to provide suggestions to improve it. In their study, Anderson et al. (2010) found that telephone reporting worked very well, but the internet and paper reports could use some performance improvements. Some of the suggestions to improve the internet reporting system include making it easier for the potential users to direct themselves through the web pages, allowing users to save the report while they are going through it in case of inability to finish entirely in one sitting, and reducing the complexity of the drop-down menu options of adverse

drug reactions. In addition, the suggested improvements for paper reporting of ADRs include allowing more space for the recording of multiple medications, redesigning the envelope so that the report fits within it more easily and having a bigger font size. Anderson et al. (2011) also make valuable suggestions, claiming that when new systems are designed for reporting adverse drug reactions, they should always be tested by potential users prior to approval of the system; this way any potential problems are identified and eliminated in advance (Anderson et al., 2011).

Kuemmerle et al. (2011) have recently investigated the global reporting of adverse drug reactions for anti-malarials, including artemisinin-based combination therapy, to the World Health Organization. They found that while this disease is a major public health problem causing nearly a million deaths annually, it is poorly controlled in many countries and the adverse drug reactions to anti-malarials and to the artemisinin-based combination therapy have a low reporting rate and that most reports were submitted by high-income, non-endemic countries. Having an understanding of the increasing availability of artemisinin-based combination therapy, the lack of sufficient information on the safety of these and other anti-malarial medications, high potential for inappropriate drug use, and many other phenomena, it is only common sense to have an adverse-drug reactions reporting system that is nationally recognized and functional. This kind of reporting system would make it possible to gather as much information as possible about what to expect from anti-malarial therapies, including artemisinin-based combination therapy, as well as other classes of medications. Kuemmerle et al. (2011) express that the very low submission rate of ADRs, very poor presence of their pharmacovigilance systems, and the enormous utilization of anti-malarial regimens observed in the sub-Saharan African countries suggest lack of human resources, absence of funds, absence or shortage of donor agencies and lack of clear reporting guidelines. These countries have great potential to contribute in understanding the possible drug

effect and events associated with anti-malarials in general, as well as with artemisinin-based combination therapy, simply due to their high utilization and necessity of such treatments. It is clear that further work must be done in these settings and it would be greatly beneficial to bring together national pharmacovigilance organizations in the non-governmental organizations, and global coordinators in order to create solutions and to address the great lag between the “rapidly growing ACT use and ensuring public health safety” (Kuemmerle et al., 2011).

According to Kessler et al. (1998), a survey of USA poison-control centers found out that about 50% of these centers reported at least one adverse drug reaction indirectly or directly to the MEDWatch during one year, at which time 27,098 cases of adverse drug reactions were reported. Only about 1% of these reported adverse drug reactions were then sent and reported to the MEDWatch. As small as this percentage may seem, it is the same as the percentage of the adverse drug reactions reported to the MEDWatch by all of the other health care professionals. Among the major reasons of failing to report a higher percentage of these ADRs to the MEDWatch system included lack of time, lack of personnel, absence of culture, and so on. It is clear that this is an issue that must continue to improve, as the lives of current and future patients depend on the efficacy and safety of these medications. While the electronic submission of adverse drug reactions reports by different drug manufacturers to Food and Drug Administration is work-in-progress, the global electronic exchange of post-marketing safety data is very hopeful (Chyka et al., 2000). While there may be certain barriers that do not create the most convenient environment for the poison-control-center employees to report adverse drug reactions to the MEDWatch, a little bit more awareness, effort, and support could help to improve the poison-control-centers, which are already a crucial part of the health care system. Maximal utilization of

these settings could have huge benefits in collecting and understanding adverse drug reactions and drug events.

In addition to under-reporting of adverse drug reactions that was observed in poison-controlled centers, Hazell et al. (2006) found wide-spread of underreporting of adverse drug reactions to spontaneous reporting systems (including both serious and severe adverse drug reactions). While the authors of this study stated of realizing that it is not possible to have a completely accurate number of the percentage of under-reporting of the ADRs, they estimated it to be around 90% or higher. This under reporting of ADRs has a direct impact on clinical knowledge of the risks and/or benefits of drugs. It is obvious that reporting ADRs is crucial and it should be approached as a fundamental duty of the health care professionals. Frequent reminders or even specific education of health care professionals might be very beneficial in improving their input in reporting adverse drug events. This 'education' could be incorporated in the continuing medical education of health care professionals (Hazell et al., 2010).

However, Lopez- Gonzales et al. (2006) suggests that professional and personal factors have a small influence in the adverse drug reactions reporting and that the attitudes and knowledge of the health care professionals are the most strongly related to high quantity and high quality reporting. Hence, they suggest that if attitudes and knowledge of professionals are factor with potential for modifications, then they may result in important public health implications. Upon ability of increasing health professionals' ability and willingness to report ADRs, patients' safety will inevitably improve and the numbers of patients being negatively affected will potentially decrease and they will become more prevented from harm.

One specific organization that has a very special role in promoting and improving the reporting of adverse drug reactions and promoting pharmacovigilance is the World Health

Organization. Its program helps in developing common standards in drug safety and monitoring, by collaborating with other organizations that are involved in pharmacovigilance [i.e., International Society of Pharmacoepidemiology (ISPE), Drug Information Association (DIA), and European Society of Pharmacovigilance (ESOP)], by organizing yearly meetings in Geneva, and by developing important word definitions that are used frequently in pharmacovigilance. WHO's positive influence in pharmacovigilance plans to continue contributing to this important field of science, according to Olson (1998), by attracting resources for follow-up and signal analysis, by increasing trust and openness between parties involved in drug safety communication and assessment of safety, and by improving the reporting to the international center (Olson, 1998).

Children belong to a population scheme that is particularly fragile and at risk of experiencing adverse drug reactions. Neubert et al. (2004) studied the probability or likelihood of licensed and unlicensed/off-label prescription drugs causing adverse drug reactions. They found that there was no statistically significant difference between the two groups. This means that the incidence of adverse drug reactions caused by licensed medications was not more than that being caused by unlicensed or off-label drugs. However, in addition they did find that off-label or unlicensed medications were more likely to have an increased risk in patients for developing adverse drug reactions. Besides drug labeling, the awareness of practitioners while prescribing drugs seemed to make a difference in the off-label or the unlicensed prescribing manner. The increased numbers of ARDs in this category of drugs were often judged as more tolerated ADRs than those caused by licensed drugs (not a statistically significant difference) (Neubert et al., 2004).

Adverse drug reactions and adverse events spontaneous reporting is an extremely important phenomena and it is crucial that every health care professional practicing medicine is aware of his or her responsibilities when it comes to this type of reporting. Overall, based on literature review, it seems that health professionals are under-reporting adverse drug reactions and drug events all over the world, regardless of the reporting system that is available to them. While it is understandable that these health care professionals are extremely busy individuals and have peoples' lives on their hands constantly, it is more than just worth it to try and develop a system of ways to promote adverse event and adverse drug reactions reporting to health care professionals. Oshikoya et al. (2009) claims that general knowledge of ADRs and how the reporting system works is insufficient among practitioners in Nigeria working in hospitals and they also suggest the necessity of continuing medical education and the need to increase awareness of the Yellow Card ADR reporting strategy (Oshikoya et al., 2009). In addition, Okezie et al. (2008) claims that the rate of ADR reporting among doctors is very low, despite their high knowledge and high observation of adverse drug reactions. They also express the need for pharmacovigilance awareness and education in hospital settings.

Attitudes of pharmacists were also evaluated and it was found that hospital pharmacists were more likely to report ARDs than community pharmacists. In addition, they found that pharmacists were much more likely to report an ADR if they thought it was serious and not likely to report something they viewed as not serious (Herdeiro et al., 2006). The overall suggestion from the entire literature review seems to conclude that the most promising way to increase the reporting of ADRs by health professionals would be through educational interventions and continuing medical education targeted at changing or improving their attitudes toward the importance of reporting ARDs and their potential outcomes.

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