

Drugs and Therapy Studies 2013; volume 3:e4

Development of a drug safety ePlatform for physicians, pharmacists, and consumers based on post-marketing adverse events

Keith B. Hoffman,¹ Brian M. Overstreet,¹ P. Murali Doraiswamy²

¹AdverseEvents Inc., Healdsburg, CA; ²Departments of Psychiatry and Medicine, Duke University Medical Center, Durham, NC, USA

Abstract

Rigorous clinical trials under the watchful eye of regulators remain the cornerstone of drug safety. However, the emergence of serious and life-threatening Adverse Events (AEs) across best-selling drug classes [sometimes many years after winning Food and Drug Administration (FDA) approval] underscores the limitations of current clinical trial processes and reinforces the need for careful postapproval pharmacovigilance. The FDA's sizeable repository of patient case reports linking AEs to approved drugs is the Adverse Event Reporting System (FAERS). We believe that open and user-friendly access to the millions of case reports in FAERS would help advance the field of post-marketing pharmacovigilance. However, FAERS data are virtually inaccessible to most physicians, pharmacists, and consumers. Accordingly, we have recently launched a big data platform (www.Adverse-Events.com) that, unlike previous efforts, provides on-demand, user-friendly, and highimpact access to FAERS data. Bringing the power of big data to regular users, such as clinicians, pharmacists, and patients, is the logical next step in the transformation of health care to a model of shared decision making between consumers and the system.

Public health impact of adverse events

Rigorous clinical trials and toxicology studies under the watchful eye of regulators remain the cornerstone of drug safety. However, the emergence of serious and lifethreatening Adverse Events (AEs) across bestselling drug classes (severe cardiac complications from sibutramine, fatal muscle-wasting syndrome from cerivastatin, increased heart attack and stroke risk from rofecoxib, etc.) many years *after* they won Food and Drug Administration (FDA) approval, and were taken by tens of thousands of consumers underscores the limitations of current clinical trial processes and reinforces the need for careful post-approval pharmacovigilance.¹⁻⁴

In fact, more than 770,000 injuries or deaths occur each year as a result of AEs linked to FDA approved drugs.5 It has been estimated that approximately 28% of such events could potentially be prevented through computerized monitoring systems.1 The FDA's repository of drugrelated AEs is the Adverse Event Reporting System (FAERS) while their AE database for medical devices is the Manufacturer and User Facility Device Experience (MAUDE).^{6,7} We believe that open and user-friendly access to the millions of case reports in FAERS would help advance the field of post-marketing pharmacovigilance. However, FAERS data are virtually inaccessible to most physicians, pharmacists, and consumers. Here we provide details concerning a newly launched big data platform (www.AdverseEvents.com) that, unlike previous efforts, provides physicians, pharmacists, and consumers with on-demand, user-friendly, and high-impact access to FAERS data.

Current state of the FAERS database

Approximately 700,000 AEs are logged into FAERS each year, across multiple therapeutic categories and ~4500 drugs.5 Despite the limitations of FAERS (e.g. variable quality of reports, inability to calculate incidence or prove causality due to the voluntary nature of reporting), regulatory agencies and the pharmaceutical industry routinely look to FAERS data for drug safety signals. Additionally, recent studies have documented the utility of FAERS for generating safety signals found within FAERS,⁸⁻¹⁸ while other investigations have compared FAERS data with AEs established through clinical trials and population studies.²⁻⁴ However, proprietary data mining and signaling tools used by regulatory agencies and major pharmaceutical companies are too expensive and complex for most people to use. Additionally, publicly available FAERS information can only be obtained through complicated data downloads by individuals familiar with relational databases. For these reasons the FAERS database has remained virtually inaccessible to most physicians, pharmacists, and consumers.

The RxFilter™ platform

In reaction to such shortcomings,

[Drugs and Therapy Studies 2013; 3:e4]

Tel. +1.707.473.8096 - Fax: +1.707.473.8096 E-mail: keith@adverseevents.com

Key words: patient safety, adverse events, side effects, drug safety, post-marketing, FDA, FAERS, AERS.

Acknowledgements: the authors wish to thank Mo Dimbil, Colin B. Erdman, and Andrea Demakas for expert data generation and editorial contributions to this manuscript.

Contributions: KBH, BMO, data collecting and analyzing; KBH, PMD, BMO, data interpretation; KBH, PMD, manuscript drafting; KBH, PMD, critical revisions.

Conflict of interests: KBH and BMO are both employees and stockholders of AdverseEvents, Inc (AEI). PMD has received research grants and served as an advisor to several pharmaceutical companies. He owns stock in Sonexa and Clarimedix (whose products are not discussed here) and in AEI.

Funding: the work was supported by of AdverseEvents, Inc.

Received for publication: 12 March 2013. Revision received: 10 May 2013. Accepted for publication: 10 May 2013.

This work is licensed under a Creative Commons Attribution NonCommercial 3.0 License (CC BY-NC 3.0).

©Copyright K.B. Hoffman et al., 2013 Licensee PAGEPress, Italy Drugs and Therapy Studies 2013; 3:e4 doi:10.4081/dts.2013.e4

AdverseEvents, Inc. (AEI) has spent the last three years analyzing and categorizing the extensive FAERS database by using a combination of computer algorithms and in-house data analysis. The platform is known as RxFilterTM, and it is making FAERS data accessible to broad groups of healthcare providers and consumers.

Two of the significant limitations that were encountered while building the RxFilterTM platform included: i) over 200,000 separate identifiers exist for the approximately 4500 FDA approved medications listed in FAERS, and ii) reports submitted to the FDA contain spelling errors, misclassifications, various data points either missing or inadequately reported, and are themselves frequently duplicated. RxFilterTM has addressed these and other issues, by employing multiple processing steps, safeguards, and manual oversight. To import data from FAERS, RxFilter uses a





framework of open source technologies such as Oracle MySQL, Python and PHP. Filtering processes include: i) a system for automated name matching which corrects for drug name misspellings and incorrect data within major fields (*i.e.*, the inclusion of dosages or routes of administration as part of the drug name field); ii) aggregation of generic and non-U.S. brand name drugs under a single brand name; iii) separation of *primary suspect* and *all suspect* designations, iv) removal of duplicate case reports; and v) identification of common adverse event and condition types.

Automated data pre-processing and scrubbing workflow provides for an initial assignment of a raw FDA FAERS drug name for approximately 95% of inputted data (within 6 hours of our receipt of those data). Computationally, this automated matching process is accomplished by string searching and phonetic matching algorithms.^{19,20} Part of the human analysis side of RxFilter includes recovery and assignment of remaining data, and reassignment of automated matches when needed (which are then corrected for future quarterly uploads). It is this combination of automated and human steps that generates matched pairs of raw FDA FAERS drug names with accepted trade or generic names. This process is applied to all FAERS data as they are uploaded to our site quarterly. The differences between what an end user sees when they download FAERS data from FDA versus how our

RxFilter platform is presented can be seen in Figure 1 which displays FAERS and RxFilter outputs.

The RxFilterTM platform is, to our knowledge, the most thoroughly optimized, userfriendly, and fully searchable drug safety database designed for use by consumers, pharmacists, and clinicians. Our quality checks indicate that the platform accurately standardizes and normalizes all reported side effects (from 1997 on) linked to over 4500 FDA approved medications. Efforts are underway to refine our platform based upon consumer and clinician feedback with features such as personalized reports and e-newsletters with the latest events in drug safety. Additionally, we plan to actively conduct quality comparison checks against other drug safety databases and academic publications.

Who has access to the RxFilter™ platform, and how do they utilize it?

AEI offers primarily a subscription model that provides limited free, and unlimited paid, access to the RxFilterTM platform. By using the site, physicians can have rapid access to FAERS information in order to supplement their sources of data to help form clinical decisions at the point of care. On the consumer side, the platform will empower users with information on adverse events that may have occurred after the launch of the drug (which even their doctors may not be aware of).

For example, a clinician, in response to a recent FDA label change, wishes to look up information on top AEs associated with Lipitor (atorvastatin). The AdverseEvents.com home page interface (Figure 2) consists of a simple search box.

Subscribers who type in the word *Lipitor* in the search box will get a screen (Figure 3) listing the total number of AEs where atorvastatin is designated as the *primary suspect* drug (arrow A), links to recent pertinent news (*e.g. February 29, 2012 FDA announces label changes for Statin drugs*), an expandable list of names (arrow B), and a table of common conditions and comparison buttons (arrow C).

Below those sections is another table (Figure 4) listing the top AEs (arrow A) and both the Proportional Reporting Ratio (PRR) and the Reporting Odds Ratio (ROR) (commonly used by drug safety professionals to look for abnormally high reporting rate of certain adverse event types) (arrows B and C).

Both PRR and ROR calculations are derived by standard formulas and specific drugs are excluded from proportionality analysis if they have less than 25 primary case reports filed over the time period studied.²¹ Figure 5 is a screen shot showing the customized searching feature that allows paid users to query any combination of: drugs, adverse events, conditions, indications, and manufacturers.

Arrow A of Figure 5 indicates the drop down menu options from *low-level* Medical Dictionary for Regulatory Activities (MedDRA)® AE terms all the way to *system organ class*, while arrow B indicates a possible collection of low-level AE terms. Figure 6 represents the case report output from the example



Figure 1. FAERS (A) and RxFilter (B) outputs.



Figure 2. The AdverseEvents.com home page interface.





search terms linking amnesia-related AEs to atorvastatin. If a user wishes to search for a specific AE (*e.g.* amnesia), subscribers can type this term into the search bar and the system will help them find the accurate AE term and list the top drugs linked to this AE. As can be seen from the Figure 7, atorvastatin is one of the top 2 agents linked to amnesia (with 823 primary suspect reports), consistent with a recent FDA warning.²²

Less commonly used drugs

The data handling for all drugs is the same. Figure 8 is a screenshot showing data for everolimus, which we selected as an example of a less commonly used drug. Everolimus is a cell growth inhibitor first approved by the FDA in 2009 that is used to treat advanced kidney and breast cancers as well as giant cell astrocytoma and pancreatic neuroendocrine tumor. As shown below, pyrexia, dysnea, diarrhea, anemia and cough are among the top AEs reported. This platform might be particularly useful for less commonly used drugs where rare AE signals that were not apparent in clinical trials might become apparent in post-marketing data after larger numbers of patients are exposed to them.

Quarterly summary updates of newest FAERS cases

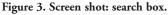
Finally, Figure 9 is page one (of seven) from our quarterly newsletter that details RxFilter analysis of the newest FAERS case reports released by FDA. Highlighted topics include: drugs with the most adverse events reported in the given quarter, drugs linked to serious outcomes, first AE reports on newly introduced drugs, and new AE trends associated with specific drugs.

Paid access programs provide: i) deeper levels of data analysis, ii) custom reports, iii) disproportionality analysis, iv) statistical tools, as well as access to v) individual case reports, vi) prescription volumes, and vi) full MedDRA hierarchy integration. These paid access platforms are designed to support competitive intelligence, drug development, and business strategies for pharmaceutical companies, healthcare organizations and insurers. More information can be found at: http://www. adverseevents.com/signup.php.

Manufacturer and user facility device experience

Manufacturer and user facility device experience (MAUDE) captures voluntary, clinical hospital, distributor, and manufacturer reports regarding medical device and information technology related AEs.⁷ Like our platform, MAUDE allows

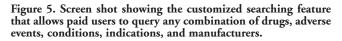




					and the second division of the second divisio
	LIPITOR Top 10 (# of Producty to	Adverse Events			ALA
Naolas Pens In Estrenery Im Articulas March Systems Montale Workers Band Ocasted Peopleblace Incessed Faringe Rabdomerylys Ocas	500 1.200 1.300 JJ	00 259 1899	3,500	4,000 4,5	80 5,000 5,5
SIDE EFFECTS MEDDRA PREFERRED TERMS	LIPITOR PRIMARY SUSPECT REPORTS	LIPITOR TOTAL REPORTS	ROR SCORE	PRR.SCORE	COMPARE TOP DRUG
Myalgia	5,413 (14%) ←A	7,309 (6%)	23.31 ← B	19.83 ←C	Compare
Pain In Extremity	2,519 (7%)	4,623 (4%)	6.32	5.95	Compare
Arthralgia	1,982 (5%)	4,100 (3%)	4.31	4.14	Campare
Muscle Spasms	1,972 (5%)	3,272 (3%)	8.36	7.92	Compare
Asthenia	1,844 (5%)	5,253 (4%)	2.97	2.87	Compare
Muscular Weakness	1,775 (5%)	2,702 (2%)	10.78	10.26	Compare
Blood Creatine Phosphokinase Increased	1,726 (5%)	2,423 (2%)	17.18	16.45	Converte
Pain	1,680 (4%)	4,813 (4%)	2.16	2.11	Compare
Fatigue	1,635 (4%)	5,192 (4%)	1.96	1.92	Compare
Rhabdomyolysis	1,538 (4%)	2,344 (2%)	16.34	15.65	Concessor 1

Figure 4. Screen shot listing the top AEs and both the Proportional Reporting Ratio and the Reporting Odds Ratio.





CALL N. MILLIN							NUMBER PERMIT	VERMANY VERMANN						
		96/27/2013		iles.	1	(10)	LIPITON	40 MG, TAGAY	CODANE TRANSFADDINE TRANSFA	ANGEORATINE SAUG INEPPECTIVE DEMOSISTERY ADMONIAL DEMOSISTERY ADMONIAL VENCES INFAUNUELT	Plan, Inc.	(15-04))	Consumer	COLOWBIA
safer.im	8798753	08/23/2012	INCOME.	YEARS	M	194	Limiton	une .	teo Data	MEMORY IMPARAENT	Pficer, Std.		Consumer	UNITED.
8011560	8796288	96320912	IN(T)A).	87 16485	'	05 kg (142.00 htt	LIPITOR	49.945	ASPIRIN, BRICKINI, PLANK, PRILOBEC TIMBICORT	Addielisi Addielisi MacArcellisi Binarroce brokholik Binarroce brokholik Binarroce brokholik Ingestuwe addityl wirkegenessi Binarrocelli Binarrocelli	Sambai, Int.	Expedited (15-Dept	Ober Health Professional	UNITED ASSOCIATE

Figure 6. Screen shot: case report output from the example search terms linking amnesia-related AEs to atorvastatin.

Review



on-line searching of data. Analyses of MAUDE's device related reports of malfunction, serious AEs, or death has yielded substantial new safety information on devices such as implantable cardioverter-defibrillators, the da Vinci surgical system, spinal cord stimulators, and even health information systems.⁷ These data enable the design of safer processes and earlier identification of risks for both consumers and clinicians, and therefore support our creation of a similar platform for drugs and biologics.

Limitations

FAERS and, accordingly, RxFilter, has limitations including: duplicate reporting, masking, amplification, incomplete information, physicians might disproportionately report effects associated with newer drugs, the influence of other drugs or factors cannot be ruled out from a given case report, reporting can be influenced by publicity and marketing, lack of true incidence rates, and accurate usage data, all of which have been described elsewhere more thoroughly.^{2,6,8,14,17,18} Despite such limitations, accumulating evidence from several hundred published studies of dozens of drugs confirms the utility of FAERS data mining for yielding new insights about drug safety signals.^{2,9-24} Nevertheless, FAERS limitations and other qualifications noted here should always be considered when using the RxFilter. We strongly recommend that patients consult with their prescribing physician before taking any

action that relates to information they find in
FAERS or our platform.

Future directions

Future work will further integrate post-marketing AE databases with electronic medical records,23,24 prescription data,2 drug interaction databases,23 and emerging biomarker and genomics data.15 The development of new algorithmsto further improve the accuracy of signal detection,^{2,19} and the development of user-friendly visual analytics and display techniques, will further enhance these systems. Combining AE data with chemical structures of drugs is also proving useful for target prediction and to engineer the development of novel therapies with better safety profiles. The impact of AE monitoring systems on patient outcomes, clinician treatment choices, and regulatory decision making will also be important to study further. Such studies will likely contribute to reducing the growing morbidity associated with serious drug safety events.

		Drugs with the most Adv	rse Events Reported	(A)(A)
				Avoices
DRUGS	# OF PATIENTS (01/01/2004/T0 08/27/2012)	DEATH	LIFE THREATENING	HOSPITALIZATIONS
	Primary Suspect	Primary Suspect	Primary Suspect	Primary Suspect
Ambien	1,173 (5%)	17 (4%)	111 (8%)	243 (39)
Lipitor	823 (3M) ←A	1 (<19)	20 (1%)	113 (190)
Chantix	799 (3%)	7 (1%)	38 (3%)	227 (3%)
Pondimin	600 (3%)	6 (1%)	10 (196)	106 (1%)
Avonex	562 (2%)	8 (2%)	1 (<1%)	278 (4%)
Neurontin	545 (29)	14 (3%)	24 (29)	84 (1%)
	531 (29)	1 (<1%)	0 (0%)	75 (1%)
Tysabri			32 (294)	121 (290)
	489 (291)	4(1%)	-P4 14 797	161 (A.16)
Tysabr) Paxil Redux	489 (2%) 464 (2%)	4 (1%) 3 (1%)	0 (0%)	49 (1%)

Figure 7. Screen shot.	Example: atorvastatin is one of the top	2
agents linked to amnes	sia with 823 primary suspect reports.	

Top 50 AFINITOR Adverse Even	its/Side Effects		Croup by NedDiA Preferred Terms (Default) # Croup						
SIDE EFFECTS MEDDRA PREFERRED TERMS	AFINITOR PRIMARY SUSPECT REPORTS	AFINITOR TOTAL REPORTS	ROR SCORE	PRR SCORE	COMPARE TOP DRUGS				
Neoplasm Malignant	642 (18%)	707 (16%)	46.66	38.31					
Death	614 (17%)	664 (15%)	6.40	5.53	Company				
Dysphoea	376 (10%)	426 (10%)	4.63	4.26	Compare				
Neoplasm Progression	310 (9%)	342 (9%)	115.95	106.62	Company				
Pyrexia	301 (8%)	382 (9%)	5.14	4.79	Company				
Fatigue	262 (7%)	327 (7%)	3.20	3.05	Company				
Diamhoea	236 (7%)	295 (7%)	3.45	3.29	Campert				
Anaemia	207 (6%)	238 (5%)	7,00	6.65	Carryson				
Nausea	193 (5%)	243 (5%)	1.57	1.54	Campara				
Cough	191 (5%)	230 (5%)	6.59	6.29	Compare				
Asthenia	179 (SW)	222 (5%)	2.93	2.64	Compare				
Volniting	165 (5%)	223 (5%)	2.07	2.02	Complete				
Pneumonia	156 (4%)	196 (4%)	3.76	3.64	Compart				
Pleural Effusion	147 (4%)	172 (4%)	11.23	10.82	Compare				
Oedema Peripheral	146 (4%)	170 (4%)	3.68	1.57	Company				
Stomatitis	145 (4%)	165 (4%)	21.39	20.58	Compare				
Decreased Appetite	132 (4%)	170 (4%)	3.66	3.56	Campara				
Haemoglobin Decreased	131 (4%)	153 (294)	6.13	5.94	Canipare				
Malaine	125 (3%)	149 (3%)	2.41	2.37	Company				
Dehydration	123 (3%)	164 (4%)	4.58	4.45	Campara				
Abdominal Pain	122 (3%)	165 (4N)	3.16	3.08	Compare				
Pneumonitis	121 (296)	145 (296)	38.61	37.36	Compare				
Bood Creatinine Increased	119 (296)	151 (294)	7.56	7.34	Chargedon				
C-reactive Protein Increased	119 (3%)	123 (JNI)	18.59	18.00	Company				
General Physical Health Deterioration	118 (JN)	136 (JN)	7.44	7,22	Compare				
Interstitial Lung Disease	116 (3%)	139 (3%)	14.01	13.61	Company				
Thrombocytopenia	101 (396)	130 (3%)	4.84	4.74	Company				

Figure 8. Screen shot showing data for everolimus, which was selected as an example of a less commonly used drug.

AdverseEvents Redefining DRUg SAFety	www.adverseevents.com
AdverseEvents M	onitor: Q3 2012
In This Issue:	
Drugs With First Reports in Q3 2012	AdverseEvents now includes all FAERS
Trending Drugs in Q3 2012	data from 1997 to

The 10 Drugs With Most Reports in Q3 2012

O3 2012

The 10 Drugs With Most Reports in Q3 2012
Serious Outcomes for the Most Reported Drugs in

Drugs With First Reports in Q3 2012

Drug Name	Primary Cases Q3	Top Adverse Event		
Zoely (estradiol; nomegestrol acetate)	13	Deep Vein Thrombosis, Pulmonary Embolism, and Urticaria		
Myrbetriq (mirabegron)	п	Drug, Ineffectiveness, Blood Glucose Increased, and Arrhythmia Hypersensitivity Anaphylactic Shock, and Drug Intolerance		
Elelyso (taliglucerase alfa)	3			
Subsys (fentanyl sublingual spray)	2	Application Site Pain, Nausea, Edema Mouth, and Pancreatic Carcinoma		
Myorisan (isotretinoin)	1	Aggression and Depression		

includes all FAERS data from 1997 to 2012. Search over 4 million records and over 500 million unique data points.

AdverseEvents, Inc. analyzed the newest adverse event reports released by the FDA's Adverse Event Reporting System (FAERS) for the partial third quarter release period of 2012, from 07/01/2012 through 08/27/2012.

Utilizing RxFilter, a proprietary data aggregation and refinement process, we analyzed the drugs with the most adverse events reported in this partial quarter, drugs with serious outcomes, new drugs reported in this partial quarter, and trends across specific drugs. The number of new, unique adverse event reports released by the FDA for this partial Q3 2012 period was 117,517.

For the partial Q3 period of 7/1/2012 -8/27/2012, there were 12,497 adverse event cases with a reported outcome of death, 4,197 adverse event cases with a reported outcome of disability, and 34,685 adverse event cases with a reported outcome of hospitalization.

Figure 9. Page one (of seven) from the quarterly newsletter that details RxFilter analysis of the newest FAERS case reports released by FDA.





Conclusions

A central tenet of the Hippocratic oath, *primum non nocere* (first, do no harm), has remained the cornerstone of medical practice for centuries. Bringing the power of big data to regular users, such as clinicians and patients, is the logical next step in the transformation of health care to a model of shared decision making between doctors, consumers, and the system.

Note

MedDRA®, the Medical Dictionary for Regulatory Activities terminology is the international medical terminology developed under the auspices of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The MedDRA® trademark is owned by IFPMA on behalf of ICH.

References

- Agency for Healthcare Research and Quality. Reducing and preventing adverse drug events to decrease hospital costs. AHRQ Publication Number 01-0020. 2001. Available from: http://www.ahrq.gov/ research/findings/factsheets/errors-safety/aderia/. Accessed on: May 2013.
- 2. Szarfman A, Tonning JM, Doraiswamy PM. Pharmacovigilance in the 21st century: new systematic tools for an old problem. Pharmacotherapy 2004;24:1099-104.
- 3. Moore TJ, Furberg CD, Glenmullen J. et al. Suicidal behavior and depression in smoking cessation treatments. PLoS One 2011;6:e27016.
- 4. Sakaeda T, Kadoyama K, Okuno Y. Statinassociated muscular and renal adverse events: data mining of the public version of the FDA adverse event reporting system. PLoS One 2011;6:e28124.

- 5. U.S. Food and Drug Administration. Reports Received and Reports Entered into AERS by Year. Available from: http://www.fda.gov/Drugs/GuidanceCompli anceRegulatoryInformation/Surveillance/A dverseDrugEffects/ucm070434.htm. Accessed: November 2012.
- 6. U.S. Food and Drug Administration. FDA Adverse Event Reporting System (FAERS), U.S. Food and Drug Administration. Available from: http://www.fda.gov/Drugs/ GuidanceComplianceRegulatoryInformati on/Surveillance/AdverseDrugEffects/defau It.htm. Accessed: November 2012.
- U.S. Food and Drug Administration. MAUDE - Manufacturer and User Facility Device Experience. Available from: http://www.accessdata.fda.gov/scripts/cdrh/ cfdocs/cfmaude/search.cfm. Accessed: May 2012.
- Hochberg AM, Hauben M. Time-to-signal comparison for drug safety data-mining algorithms vs. traditional signaling criteria. Clin Pharmacol Ther 2009;6:600-6.
- 9. Poluzzi E, Raschi E, Moretti U, De Ponti F. Drug-induced torsades de pointes: data mining of the public version of the FDA Adverse Event Reporting System (AERS). Pharmacoepidemiol Drug Saf 2009;18:512-8.
- Robertson HT, Allison DB. Drugs associated with more suicidal ideations are also associated with more suicide attempts. PLoS One 2009;4:e7312.
- 11. Bailey S, Singh A, Azadian R, et al. Prospective data mining of six products in the US FDA Adverse Event Reporting System: disposition of events identified and impact on product safety profiles. Drug Saf 2010;33:139-46.
- Harpaz R, Chase HS, Friedman C. Mining multi-item drug adverse effect associations in spontaneous reporting systems. BMC Bioinformatics 2010;11 Suppl 9:S7.
- Moore TJ, Glenmullen J, Furberg CD. Prescription drugs associated with reports of violence towards others. PLoS One 2010;5:e15337.

- 14. Wang HW, Hochberg AM, Pearson RK, Hauben M. An experimental investigation of masking in the US FDA adverse event reporting system database. Drug Saf 2010;33:1117-33.
- 15. Takarabe M, Kotera M, Nishimura Y, et al. Drug target prediction using adverse event report systems: a pharmacogenomic approach. Bioinformatics 2012;28:i611-8.
- Tamura T, Sakaeda T, Kadoyama K, Okuno Y. Aspirin- and clopidogrel-associated bleeding complications: data mining of the public version of the FDA adverse event reporting system, AERS. Int J Med Sci 2012;9:441-6.
- Chen HC, Tsong Y, Chen JJ. Data mining for signal detection of adverse event safety data. J Biopharm Stat 2013;23:146-60.
- Harpaz R, Dumouchel W, Lependu P, et al. Performance of pharmacovigilance signaldetection algorithms for the FDA Adverse Event Reporting System. Clin Pharmacol Ther 2013;93:539-46.
- 19. Boyer RS, Moore JS. A fast string searching algorithm. Comm ACM 1977;20:762-72.
- Knuth DE. The art of computer programming, Volume 3: sorting and searching. Reading: Addison-Wesley; 1998. pp 391-392.
- Wilson AM, Thabane L, Holbrook A. Application of data mining techniques in pharmacovigilance. Br J Clin Pharmacol 2004;57:127-34.
- 22. U.S. Food and Drug Administration. FDA Drug Safety Communication: Important safety label changes to cholesterol-lowering statin drugs. Available from: http://www.fda.gov/Drugs/DrugSafety/ucm 293101.htm. Accessed: November 2012.
- Tatonetti NP, Ye PP, Daneshjou R, et al. Data-driven prediction of drug effects and interactions. Sci Transl Med 2012;4: 125ra31.
- 24. Harpaz R, Vilar S, Dumouchel W, et al. Combing signals from spontaneous reports and electronic health records for detection of adverse drug reactions. J Am Med Inform Assoc 2013;20:413-9.