E-pharmacovigilance: development and implementation of a computable knowledge base to identify adverse drug reactions

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Adverse drug events are a significant burden for health care systems.
- Currently used pharmacovigilance methods are mostly retrospective and do not allow for an instant patient benefit.
- Specificity of electronic ADR detection systems is too low causing over-alerting and alert fatigue.

WHAT THIS STUDY ADDS

- Medical and pharmaceutical knowledge as given in the narrative of a SmPC document as well as patient's individual medical data as stored in Hospital Information Systems can be standardized using the same terminologies.
- A contextual linkage of semantically enriched drug information enhances specificity of electronic ADR monitoring systems and will reduce ADR overalerting.
- Laboratory data are valuable for prospective real time ADR monitoring.

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Keywords

adverse drug reaction, adverse drug event, ADR reporting system, computer-assisted pharmacovigilance, decision support systems, knowledge base

Received

7 December 2012

Accepted

20 March 2013

AIMS

Computer-assisted signal generation is an important issue for the prevention of adverse drug reactions (ADRs). However, due to poor standardization of patients' medical data and a lack of computable medical drug knowledge the specificity of computerized decision support systems for early ADR detection is too low and thus those systems are not yet implemented in daily clinical practice. We report on a method to formalize knowledge about ADRs based on the Summary of Product Characteristics (SmPCs) and linking them with structured patient data to generate safety signals automatically and with high sensitivity and specificity.

METHODS

A computable ADR knowledge base (ADR-KB) that inherently contains standardized concepts for ADRs (WHO-ART), drugs (ATC) and laboratory test results (LOINC) was built. The system was evaluated in study populations of paediatric and internal medicine inpatients.

RESULTS

A total of 262 different ADR concepts related to laboratory findings were linked to 212 LOINC terms. The ADR knowledge base was retrospectively applied to a study population of 970 admissions (474 internal and 496 paediatric patients), who underwent intensive ADR surveillance. The specificity increased from 7% without ADR-KB up to 73% in internal patients and from 19.6% up to 91% in paediatric inpatients, respectively.

CONCLUSIONS

This study shows that contextual linkage of patients' medication data with laboratory test results is a useful and reasonable instrument for computer-assisted ADR detection and a valuable step towards a systematic drug safety process. The system enables automated detection of ADRs during clinical practice with a quality close to intensive chart review.

Introduction

Adverse drug reactions (ADRs) account for up to 106 000 deaths in the United States annually [1]. The national cost of preventable in-hospital events alone has been estimated to be more than \$US 2 billion [2, 3]. The necessity for ADR surveillance systems became obvious after the thalidomide tragedy in the 1960s [4]. In recent years detection and reporting of ADRs has become an important component of monitoring and evaluating activities performed in hospitals [5–9].

Mandatory spontaneous reporting is the general standard of ADR detection and still the most commonly used method to detect ADRs in hospitals. However, although an invaluable signal detection instrument, spontaneous ADR reporting is associated with under-reporting, susceptibility for bias (e.g. influences by media coverage) and missing denominator data to calculate incidences [10–12]. Another common approach for ADR detection in hospitals is manual chart review, the gold standard method in pharmacoepidemiology. It is a very precise but also time-consuming instrument involving high staff expenses [13–16]. Similar to spontaneous reporting it is carried out retrospectively and thus there is no possibility for early interventions in favour of patient safety.

In contrast, a prospective system electronically participating in routine clinical data flow would have the advantage that potential ADRs could be identified early before exacerbation of the clinical condition of a patient and thus provide an instant benefit for the individual patient.

Laboratory data have been identified as appropriate ADR signals [13, 17–20]. They are available in hospital information systems (HIS) concurrently with the treatment process and can be prospectively and continuously monitored. Those systems have shown to be very sensitive to detect patients with ADRs, but specificity is very low [21, 22]. Thus too many signals are generated which hampers the acceptance by clinicians and thus the implementation in clinical routine.

To overcome this problem, less and more specific signals have to be presented to the treating clinicians. However, in order to generate patient specific ADR signals

unconnected and heterogeneous data sources such as patients’ medical history, prescribed medication and laboratory test results as well as general information on the prescribed drugs (medical knowledge) have to be linked [6, 17, 18, 23, 24]. Besides the insufficient standardization of these data sources the major problem is the missing contextual link between the available clinical data, usually stored in HIS and/or electronic medical records (EMR) and computable medical knowledge bases [25, 26].

In this manuscript we report on a method to crosslink patient data available in a HIS with standardized knowledge on drugs in such a way that they can be processed and used to generate highly specific, individual ADR signals. The objective was to convert knowledge of ADRs available from plaintext drug information into computable knowledge formats using standardized medical classifications (e.g. ATC, LOINC, WHO-ART). Furthermore we implemented this application into clinical routine and compared the signals generated with intensive chart review to determine the potential sensitivity and specificity of the system and thus the impact of this approach on signal quality.

Methods

ADR knowledge base (ADR-KB)

In order to obtain computable information on drug specific ADRs a computable ADR knowledge base (ADR-KB) was developed. The underlying database contains formalized information on ADRs which can be stated by laboratory parameters. ADR-KB comprises of three basic concepts (drugs, ADR, laboratory data) mapped to classifications such as WHO Adverse Reaction Terminology (WHO-ART), Logical Observation Identifiers Names and Codes (LOINC), an international nomenclature for identifying laboratory and clinical observations, and the WHO Anatomical Therapeutic Chemical Classification System (ATC) to standardise drug information. Details of the three concepts are given in Table 1.

The medical-pharmaceutical knowledge of ADR-KB was obtained from the official German Summary of Product Characteristics (SmPCs) [27]. Specially trained phy-

Table 1

Description of terminologies used in ADR-KB

<p>WHO – Adverse Reaction Terminology (WHO-ART) [38] has been developed over more than 30 years to serve as a basis for rational coding of adverse reaction terms. Because new drugs and new indications produce new terms which need to be incorporated, the structure of the terminology is flexible enough to allow for additions whilst maintaining the structure of the terminology and without losing established relationships. The basic logic allowing such flexibility is a hierarchical structure starting with body system/organ level, within which there are groupings (general or high level terms), which are useful for the broadest view of drug problems.</p>
<p>The Anatomical Therapeutic Chemical (ATC) [41] classification system was developed as an international standard for drug utilisation studies. Drugs are attributed to different classes according to the organ or system on which they act and their chemical, pharmacological and therapeutic properties.</p>
<p>Logical Observation Identifiers Names and Codes (LOINC) [42] are universal identifiers for laboratory and other clinical observations. LOINC laboratory test results are named in a consistent and comprehensive manner, according to the attributes component, property, time, system or specimen, scale or precision and method. Each unique combination of these six parts constitutes a unique laboratory result and is given a unique LOINC identity code.</p>

Table 2

Standard categories of ADR frequency recommended by CIOMS and commonly used in SmPCs

ADR frequency categories	
Very common	≥10%
Common	≥1% and <10%
Uncommon	≥0.1% and <1%
(Very) rare	<0.1%

Table 3

Examples for contextual linkage of WHO-ART to LOINC

ADR	WHO – ART ADR number	Sequence number	Laboratory test	LOINC
Cholestatic hepatitis	351	1	S-aspartate-aminotransferase	1920-8
			S-alanine-aminotransferase	1742-6
			Bilirubin (total)	1975-2
			Bilirubin (direct)	15152-2
			γ-glutamyltransferase	2324-2
			Alkaline phosphatase	6768-6
Myositis	748	1	S-creatinine phosphokinase	2157-6
			S-myoglobin	2639-3
Nephritis	607	1	S-creatinine	14682-9
			U (sed)-cylinder, hyalin	5807-3

sicians and pharmacists manually examined as knowledge engineers the SmPC plaintext information of 700 drugs (linked with ATC) and extracted information on ADRs related to these drugs using the WHO-ART classifications.

These identified ATC–WHO-ART relationships were assessed and structured according to the standard categories of ADR frequency recommended by the Council for International Organizations of Medical Sciences (CIOMS). (Table 2) ADRs without any frequency information in the SmPCs were assessed as ‘frequency not known’.

Secondly, a contextual link between the drugs coded using ATC, ADRs related to this drug coded by WHO-ART and laboratory parameters affected by these ADRs classified by LOINC was established by the knowledge engineers.

The basic assumption of this contextual linkage was that ADRs can be identified and expressed by one or more laboratory test results.

For this purpose, suitable ADRs extracted from the plain-text information and structured with WHO-ART were linked to laboratory tests represented by LOINC names independent of their relationship to a drug (ATC).

Each WHO-ART–LOINC relationship was evaluated carefully by the knowledge engineers and approved by medical experts working in the fields of hepatology, gastroenterology, endocrinology, haemato-oncology, bleeding and clotting disorders, nephrology, pulmonology and

medical chemistry (see acknowledgments for details). Examples of WHO-ART–LOINC relationships are given in Table 3.

Implementation of ADR-KB into the HIS

The purpose of the ADR-KB is to be connected with patients’ individual data from an EMR in order to enable the creation of patient specific alerts for potential ADRs based on the patient’s prescribed medicine and laboratory test results outside predefined ranges. This information is usually available within the HIS and thus ADR-KB was integrated into the local clinical information system.

To achieve a semantic integration between ADR-KB and patient’s clinical data in the HIS all laboratory tests measured in the hospitals laboratory information system (LIS) were mapped to LOINC.

Furthermore, since at the time of this study patient medication was not yet electronically prescribed routinely, this procedure was supplemented during the study. Thus all patient medication data were documented electronically on a daily basis. Generally, in our hospital, prescriptions are made either by commercial or generic name. If commercial names were given these were translated into the generic names and their corresponding ATC codes using a commercially available drug database (ABDA). If the generic name was given this was linked with the corresponding ATC code only.

For the purpose of this evaluation patients’ medication data and laboratory findings as well as diagnoses, potential ADRs and the ADR-KB were stored in a separate patient database. Rules for signal generation were also recorded in this database. A web-based user interface was developed to present these data to treating physicians within the local HIS.

Evaluation

A preliminary evaluation of the ADR-KB was conducted in two study populations consisting of paediatric and internal medicine in-patients from the University Hospital Erlangen-Nuremberg.

These patient populations were evaluated within previous pharmacovigilance studies using intensive chart review to identify ADRs [21, 22]. As intensive chart review is known to identify 100% of ADRs we could evaluate how many of those ADRs the ADR-KB would have identified and thus calculate its sensitivity and specificity [14].

The sensitivity of the systems was defined as the number of ADR positive patients alerted by at least one signal in relation to the total number of ADR positive patients.

The specificity of the system was defined as the number of all non-ADR patients not alerted by any signal in relation to the total number of non-ADR patients.

In addition, sensitivity and specificity were calculated taking different ADR frequency categories (very common, common, etc.) as defined in SmPCs into account.

Figure 1

Knowledge extraction and contextual linkage of ADR-KB and patients' data from EHRs as available in the HIS

Results

Contextual links in ADR knowledge base (ADR-KB)

Based on the drugs most frequently used in our hospital (hospital drug formulary) 700 generic drugs were screened by knowledge engineers by reviewing the SmPCs with respect to ADRs. About 262 different ADRs were retrieved and linked to a total of 212 different LOINC terms by a *many to many* ($m : n$) relationship. A total of 396 ATC codes contained at least one ADR relationship, which could be expressed by laboratory tests.

On average one WHO-ART term was associated with three LOINC names (minimum 1–maximum 9) resulting in a relationship of one ATC code with 11 LOINC names (minimum 0–maximum 53). In Figure 1 the schematic structure of ADR-KB is shown.

Patient database

Internal medicine The study population from our department of internal medicine comprised of 474 admissions. In 460 out of these 474 admissions, 39819 laboratory tests represented by 206 different LOINC (pathologic: 9043 tests/57 LOINC names) were processed during the study

period. On average 87 laboratory tests were performed per admission (minimum 1, maximum 968, $SD \pm 85.4$).

Three thousand seven hundred and forty-two drug prescriptions represented by 287 different ATC codes were made for 411 patients during the study period. Patients received an average of nine different drugs (minimum 0, maximum 49, $SD \pm 6.39$). The drugs most often prescribed were omeprazole ($n = 253$) followed by pethidine ($n = 208$) and midazolam ($n = 195$). More details of this study are described elsewhere [21].

In 74 ADR positive admissions, 10417 laboratory tests (1584 pathologic) were performed. An evaluation of the computerized monitoring system purely on laboratory data with no link to the prescribed medicines revealed that the sensitivity of the system was as high as 91%. However, specificity was only found to be 23% [21].

After implementation and use of ADR-KB, i.e. signals were only generated if the patient had a drug potentially impacting on the laboratory test results, specificity increased to 32.2% if all ADR information in the new drug database, independent of their reported frequency category, were used and 72.6% if only common ADRs were taken into consideration. Corresponding sensitivity was 88.2% and 57.9%, respectively. Other frequency categories

Figure 2

Changes in sensitivity and specificity after implementation of ADR-KB while using different frequency categories in internal and paediatric patients. *all reported ADRs included are independent of the frequency category. ■, sensitivity internal; ■, sensitivity paediatric; ■, specificity internal; ■, specificity paediatric

and their impact on sensitivity and specificity are shown in Figure 2.

Paediatrics Our paediatric study population comprised of 439 admissions (396 patients) [22]. Patients spent an average of 5.2 days (median 3 days, SD ± 18.5) in hospital and had a mean age of 6.1 years (median 4 years, SD ± 6.6). A total of 1999 drugs were prescribed to 379 paediatric patient admissions (median 4 drugs per admission, minimum 1, maximum 28, SD ± 4.3) representing 225 different ATC codes. Drugs most often prescribed were paracetamol ($n = 130$), vitamin D₃/sodiumfluoride ($n = 92$) and ibuprofen ($n = 90$). More details of this study are described elsewhere [21].

Overall 27434 laboratory tests expressed in 139 different LOINC concepts (pathologic: 2509 tests/24 LOINC definitions) were ordered for the study population during the study period. On average 50 laboratory tests (min = 3, max = 1099, SD ± 84.37) were ordered in 406 admissions. In 59 ADR positive admissions 6442 laboratory tests (662 pathologic) were performed. The evaluation of the computerized system purely on laboratory data with no link to the prescribed medicines revealed that the sensitivity of the system was as high as 90.3%. However, specificity was only found to be 19.6%.

After implementation of ADR-KB the specificity improved to 53.1% whilst and use sensitivity decreased to 82.3% only if all ADRs in ADR-KB were considered. In the

case where only common ADRs were taken into account specificity increased up to 80% and sensitivity was found to be 50%. Other frequency categories and their impact on sensitivity and specificity are shown in Figure 2.

Discussion

This study introduces an innovative computer-based method to generate patient specific safety information on drugs which overcomes the usual problem of overalerting and alert fatigue. We could show that the method of linking laboratory findings with drug information and potential ADRs by using medical terminological systems and thus conceptualising medical knowledge enables an effective detection of ADRs in hospitals. The effectiveness of the system was evaluated in 970 admissions (496 admissions to the paediatric department and 474 admissions to the department of internal medicine, 67253 routinely requested laboratory test results and 5747 prescribed medications. The data obtained from the paediatric patients are comparable with those from the internal medicine patients. In both populations an increase in specificity was observed.

Increasing specificity to overcome alert fatigue

Until now in the field of computerized pharmacovigilance, low specificity of signals indicating potential ADRs has impeded the implementation of computerized monitoring systems in routine clinical practice except under epidemiological study conditions [21, 23, 28, 29].

Too many false positive signals cause physicians to become tired of reacting to those signals. This phenomenon following overalerting is commonly known as alert fatigue [30–32].

The purpose of our novel approach was to generate patient specific signals based on the medicine actually prescribed to the patients in a tailor-made and up to date manner.

Laboratory data have been identified as valuable signals for the detection of ADRs. However, assessing laboratory test results out of the context of patients' drug therapy solely provides a wide range of unspecific signals.

Smithburger *et al.* have, for instance, shown that for commonly available drug–drug interaction databases more patient specific information is needed to avoid alert-fatigue [33].

In our approach we put laboratory data in context to the drugs which may according to their known pharmacological characteristics impact on the various test results. Thus an ADR alert will only be generated if the patient has (i) a pathologic laboratory test result and (ii) a medication that may cause a change of the respective laboratory test result.

Our preliminary evaluation showed that in both paediatric and internal medicine patients, the specificity of the signal generation increases significantly. In parallel the

sensitivity, i.e. the proportion of ADR positive patients identified, remained high. This is in contrast to previous systems which did not have a contextual link between patient individual data, i.e. medication. In those systems sensitivity usually decreased if rules were implemented to increase specificity [21, 22].

Broad coverage of ADRs

Methods currently used by clinical application systems for the detection of ADRs vary greatly not at least because they have to be adapted to the specific characteristics of each hospital or clinical environment. There are two major approaches which to date are used by computerized monitoring systems for the early detection of ADRs. On the one hand there are prospectively working software solutions that search for sentinel words or 'Triggers' (e.g. the word 'hypoglycaemia') in patients' EHRs [34–36] whereas, on the other hand, there are those systems which are based on prospective clinical signals generated by laboratory information systems (automatic laboratory signals, ALS) [21, 22, 37].

The computer-assisted assessment of laboratory data in view of ADRs so far has proven to be sensitive for real-time detection of ADRs in routine clinical practice. However, it is limited to some events expressed by the laboratory information. Ramirez *et al.* report on the successful implementation of a monitoring system for the detection of serious adverse drug reactions (SADRs) [19]. However, only 30% of the signals had a direct association with an ADR. Because of the lack of a gold standard methodology the authors were not able to calculate sensitivity and specificity of the system. Nevertheless, the symptoms detectable by clinical information systems (e.g. agranulocytosis, pancytopenia etc.) were limited and did not represent the variety of possible ADRs. Similarly, 'trigger systems' are limited to certain events which have to be pre-defined before implementing the system such as 'hypoglycaemia', 'toxicity', etc. Both methods use an not really systematic approach to detect potential ADRs and thus are not able to cover the full range of possible ADRs.

In contrast, our ADR-KB contains clinical drug knowledge provided by the SmPC of a drug and systematically links this information with corresponding laboratory data. The basic assumption for establishing this ADR-KB was that ADRs such as hepatotoxicity, gastrointestinal bleeding, electrolyte imbalance, overdosing of phenprocoumon, hypoglycaemia, agranulocytosis, etc. as given in the SmPCs can be stated by laboratory test results, i.e. increasing liver related enzymes (GGT, AST, ALT), red or white blood cell count, coagulatory parameters [13, 17, 18, 20].

Of course we are aware that ADRs causing clinical symptoms (e.g. diarrhoea, hair loss, emesis) are difficult to map with laboratory test results. However, these clinically apparent ADRs do not necessarily have to be detected by computerized monitoring systems as they are seen by the physicians and the medical staff anyway. Nevertheless, by

introducing WHO ART [38] codes as an expression of ADRs in our ADR-KB, a linkage with patient symptoms would also be possible as long as those symptoms are adequately stored in the HIS and coded or linked to WHO-ART codes.

Within this, our approach has the potential to cover the entire range of ADRs and is not limited to some single events.

Management of medical knowledge

One prerequisite for our approach is to transfer information available in the free-text of SmPC into a computable and semantically enriched knowledge format.

This so called medical knowledge processing has been intensively discussed, especially in general medical computer sciences within the last few years [31, 39, 40].

Unstructured information about drugs such as wanted and unwanted effects, dosage recommendations, indications and contraindications, are available in a huge number of media like databases, books and journal articles. Thus, most of this knowledge is hardly suitable for computer-assisted processing and building links to other databases.

We formalized the knowledge about ADRs by introducing semantic metadata using established and commonly used medical terminological systems. The use of terminologies also enabled the establishment of a contextual cross-link to patients' clinical data.

The ATC terminological system that was chosen for coding drugs provides a global standard for identification of drugs and is suitable for clinical prescribing. It is based on the work of the WHO Collaborating Centre for Drug Statistics Methodology in Oslo. The codes are maintained regularly and all new human drugs will be supplemented accordingly [41].

A basic assumption for using ATC codes is that medication prescribed and documented by its trade name in the EHR is easily mapped to ATC codes. This is already offered by most of the drug-databases currently available in Germany. Consequently, these data can be linked with our ADR-KB and be utilized for the development of patient specific information processing.

Similarly, LOINC offers a set of universal identification codes and nomenclature to identify laboratory procedures and test results. Unfortunately, although widely established, LOINC has not been implemented yet into our routine clinical laboratory system. Therefore more than 2500 laboratory tests provided by our laboratories were coded manually using this standard set of names and codes [42].

Surprisingly, only 212 LOINC were required to represent the ADRs extracted from the plain text information of 700 generic substances coded in ATC.

Nevertheless medical knowledge is dynamically and continuously increasing [40]. It will be essential to ensure that our ADR-KB will be regularly maintained and evaluated in future. On the other hand the cost-effective way of this approach may not be abrogated by time-consuming

maintenance procedures. Therefore establishing a professional editorial system for the easy updating and maintaining of standardized medical knowledge will be an objective for widespread implementation of the system in HIS.

Early detection

One major disadvantage of already established pharmacovigilance systems is that signals are identified and assessed retrospectively, i.e. there is no direct benefit for the patient.

In contrast, utilizing laboratory data would allow the early identification of a potential ADR for two reasons [20]. Firstly, laboratory test results are immediately available in the HIS after the test results are known and thus provide a realistic picture of the patient's clinical condition. Secondly, the occurrence of an ADR is usually not a sudden reaction. It takes some time to develop before clinical manifestation. Laboratory data enable the very early identification of potential ADRs, e.g. any change in liver enzymes can be detected even it would not yet be considered pathologic if it is seen on its own. We have previously introduced alerts for differential values (DELTA values) to identify trends and could show that they significantly increased specificity of the signals. However, assessing them on their own leads to a decrease in sensitivity [21, 22].

Due to the nature of this analysis which simulated the signal generation retrospectively we could not determine the extent to which ADRs would have been identified early and the implications for the patients.

Conclusion

In conclusion, this study shows that contextual linkage of patients' medication data to laboratory test results implemented as a computable knowledge base could be a useful instrument for the data-driven detection of ADRs and the first step towards systematic pharmacovigilance. This system enables computer-assisted detection of adverse drug events with quality close to the gold standard intensive chart review.

However, the impact of the described system in everyday practice, its time and cost- saving effects, and its influence on clinical decision making, has to be evaluated more accurately.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare no support from any organization for the submitted work, no financial relationships with any organization that might have an interest in the submitted work in the

previous 3 years and no other relationships or activities that could appear to have influenced the submitted work.

This study was supported by grants from the German Israeli Foundation (GIF), Bayerisches Staatsministerium 'Bayern aktiv', Marohn Stiftung and Doerenkamp Professorship for Innovations in Animal and Consumer Protection.

We would like to acknowledge Dr M. Radespiel-Tröger (Department of Medical Informatics, Biometry and Epidemiology) for his support in statistics and Professor M. Levy (Hadassah University Jerusalem) for the longtime co-operation and correction of the manuscript.

Furthermore we acknowledge Professor Dr Schuppan¹ (Hepatology), Professor Dr Schneider² (Gastroenterology), Professor Dr Lohmann³ (Endocrinology), Professor Dr Kalden⁴ (Haematology and clotting and bleeding disorders, Professor Dr Hilgers⁴ (Nephrology), Professor Dr Ficker⁵ (Pulmonology) and Dr Parsch⁴ (Laboratory physician) for their support.

REFERENCES

- 1 Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. *JAMA* 1998; 279: 1200–5.
- 2 Bates DW, Spell N, Cullen DJ, Burdick E, Laird N, Petersen LA, Small SD, Sweitzer BJ, Leape LL. The costs of adverse drug events in hospitalized patients. Adverse Drug Events Prevention Study Group. *JAMA* 1997; 277: 307–11.
- 3 Classen DC, Pestotnik SL, Evans RS, Lloyd JF, Burke JP. Adverse drug events in hospitalized patients. Excess length of stay, extra costs, and attributable mortality. *JAMA* 1997; 277: 301–6.
- 4 Curran WJ. The thalidomide tragedy in Germany: the end of a historic medicolegal trial. *N Engl J Med* 1971; 284: 481–2.
- 5 Almenoff JS. Innovations for the future of pharmacovigilance. *Drug Saf* 2007; 30: 631–3.
- 6 Bousquet C, Henegar C, Louet AL, Degoulet P, Jaulent MC. Implementation of automated signal generation in pharmacovigilance using a knowledge-based approach. *Int J Med Inform* 2005; 74: 563–71.
- 7 Castro-Pastrana LI, Carleton BC. Improving pediatric drug safety: need for more efficient clinical translation of pharmacovigilance knowledge. *J Popul Ther Clin Pharmacol* 2011; 18: e76–e88.
- 8 Chazard E, Ficheur G, Bernonville S, Luyckx M, Beuscart R. Data mining to generate adverse drug events detection rules. *IEEE Trans Inf Technol Biomed* 2011; 15: 823–30.
- 9 Eckstrand JA, Habib AS, Williamson A, Horvath MM, Gattis KG, Cozart H, Ferranti J. Computerized surveillance of opioid-related adverse drug events in perioperative care: a cross-sectional study. *Patient Saf Surg* 2009; 3: 18.
- 10 Hazell L, Shakir SA. Under-reporting of adverse drug reactions : a systematic review. *Drug Saf* 2006; 29: 385–96.
- 11 Neubert A. Pharmacovigilance in pediatrics: current challenges. *Paediatr Drugs* 2012; 14: 1–5.
- 12 Guedat MG, Gouraud A, Ramiah T, Demaziere J, Delanoy B, Vial T, Leboucher G, Charpiat B. [Clinical pharmacy and pharmacovigilance over a period of nine years in hospital]. *Therapie* 2012; 67: 243–50.
- 13 Dormann H, Muth-Selbach U, Krebs S, Criegee-Rieck M, Tegeder I, Schneider HT, Hahn EG, Levy M, Brune K, Geisslinger G. Incidence and costs of adverse drug reactions during hospitalisation: computerised monitoring versus stimulated spontaneous reporting. *Drug Saf* 2000; 22: 161–8.
- 14 Murff HJ, Patel VL, Hripcsak G, Bates DW. Detecting adverse events for patient safety research: a review of current methodologies. *J Biomed Inform* 2003; 36: 131–43.
- 15 O'Neil AC, Petersen LA, Cook EF, Bates DW, Lee TH, Brennan TA. Physician reporting compared with medical-record review to identify adverse medical events. *Ann Intern Med* 1993; 119: 370–6.
- 16 Wysowski DK, Swartz L. Adverse drug event surveillance and drug withdrawals in the United States, 1969–2002: the importance of reporting suspected reactions. *Arch Intern Med* 2005; 165: 1363–9.
- 17 Forsstrom JJ, Gronroos P, Irjala K, Heiskanen J, Torniaainen K. Linking patient medication data with laboratory information system. *Int J Biomed Comput* 1996; 42: 111–6.
- 18 Gronroos P, Irjala K, Heiskanen J, Torniaainen K, Forsstrom JJ. Using computerized individual medication data to detect drug effects on clinical laboratory tests. *Scand J Clin Lab Invest Suppl* 1995; 222: 31–6.
- 19 Ramirez E, Carcas AJ, Borobia AM, Lei SH, Pinana E, Fudio S, Frias J. A pharmacovigilance program from laboratory signals for the detection and reporting of serious adverse drug reactions in hospitalized patients. *Clin Pharmacol Ther* 2010; 87: 74–86.
- 20 Schiff GD, Klass D, Peterson J, Shah G, Bates DW. Linking laboratory and pharmacy: opportunities for reducing errors and improving care. *Arch Intern Med* 2003; 163: 893–900.
- 21 Dormann H, Criegee-Rieck M, Neubert A, Egger T, Levy M, Hahn EG, Brune K. Implementation of a computer-assisted monitoring system for the detection of adverse drug reactions in gastroenterology. *Aliment Pharmacol Ther* 2004; 19: 303–9.
- 22 Neubert A, Dormann H, Weiss J, Criegee-Rieck M, Ackermann A, Levy M, Brune K, Rascher W. Are computerised monitoring systems of value to improve pharmacovigilance in paediatric patients? *Eur J Clin Pharmacol* 2006; 62: 959–65.
- 23 Bates DW, Evans RS, Murff H, Stetson PD, Pizziferri L, Hripcsak G. Detecting adverse events using information technology. *J Am Med Inform Assoc* 2003; 10: 115–28.
- 24 Seger AC, Jha AK, Bates DW. Adverse drug event detection in a community hospital utilising computerised medication and laboratory data. *Drug Saf* 2007; 30: 817–24.

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- 25** Chalmers RJ. Health care terminology for the electronic era. *Mayo Clin Proc* 2006; 81: 729–31.
- 26** Dudeck J. Aspects of implementing and harmonizing healthcare communication standards. *Int J Med Inform* 1998; 48: 163–71.
- 27** German medicinal product act (Drug Law). 2011. Available at http://www.gesetze-im-internet.de/englisch_amg.html (last accessed 2 July 2013).
- 28** Classen DC, Pestotnik SL, Evans RS, Burke JP. Description of a computerized adverse drug event monitor using a hospital information system. *Hosp Pharm* 1992; 27: 774, 776–779, 783.
- 29** Jha AK, Kuperman GJ, Teich JM, Leape L, Shea B, Rittenberg E, Burdick E, Seger DL, Vander VM, Bates DW. Identifying adverse drug events: development of a computer-based monitor and comparison with chart review and stimulated voluntary report. *J Am Med Inform Assoc* 1998; 5: 305–14.
- 30** Jung M, Riedmann D, Hackl WO, Hoerbst A, Jaspers MW, Ferret L, Lawton K, Ammenwerth E. Physicians' perceptions on the usefulness of contextual information for prioritizing and presenting alerts in computerized physician order entry systems. *BMC Med Inform Decis Mak* 2012; 12: 111.
- 31** Kuperman GJ, Bobb A, Payne TH, Avery AJ, Gandhi TK, Burns G, Classen DC, Bates DW. Medication-related clinical decision support in computerized provider order entry systems: a review. *J Am Med Inform Assoc* 2007; 14: 29–40.
- 32** van der Sijs H, Aarts J, Vulto A, Berg M. Overriding of drug safety alerts in computerized physician order entry. *J Am Med Inform Assoc* 2006; 13: 138–47.
- 33** Smithburger PL, Buckley MS, Bejian S, Burenheide K, Kane-Gill SL. A critical evaluation of clinical decision support for the detection of drug-drug interactions. *Expert Opin Drug Saf* 2011; 10: 871–82.
- 34** Franklin BD, Birch S, Schachter M, Barber N. Testing a trigger tool as a method of detecting harm from medication errors in a UK hospital: a pilot study. *Int J Pharm Pract* 2010; 18: 305–11.
- 35** Matlow AG, Cronin CM, Flintoft V, Nijssen-Jordan C, Fleming M, Brady-Fryer B, Hiltz MA, Orrbine E, Baker GR. Description of the development and validation of the Canadian Paediatric Trigger Tool. *BMJ Qual Saf* 2011; 20: 416–23.
- 36** Rozich JD, Haraden CR, Resar RK. Adverse drug event trigger tool: a practical methodology for measuring medication related harm. *Qual Saf Health Care* 2003; 12: 194–200.
- 37** Haffner S, von Laue N, Wirth S, Thurmann PA. Detecting adverse drug reactions on paediatric wards: intensified surveillance versus computerised screening of laboratory values. *Drug Saf* 2005; 28: 453–64.
- 38** World Health Organization. WHO-adverse reaction terminology (WHO-ART). 2003. Available at <http://www.unc-products.com/graphics/3149.pdf> (last accessed 2 July 2013).
- 39** Abidi SS. Knowledge management in healthcare: towards 'knowledge-driven' decision-support services. *Int J Med Inform* 2001; 63: 5–18.
- 40** Montani S, Bellazzi R. Supporting decisions in medical applications: the knowledge management perspective. *Int J Med Inform* 2002; 68: 79–90.
- 41** WHO Collaborating Centre for Drug Statistics Methodology. Anatomical Therapeutic Chemical (ATC) classification. 2004. Available at <http://www.whocc.no/atcddd/> (last accessed 2 July 2013).
- 42** The Regenstrief Institute. Logical observation identifiers names and codes (LOINC®). 2004. Available at <http://www.loinc.org> (last accessed 2 July 2013).