Established in 1871
Swiss Medical Weekly
Formerly: Schweizerische Medizinische Wochenschrift
The European Journal of Medical Sciences

Original article | Published 10 February 2012, doi:10.4414/smw.2012.13522
Cite this as: Swiss Med Wkly. 2012;142:w13522

Frequency and nature of drug-drug interactions in a Swiss primary and secondary acute care hospital

Marc Oertle

Spital Thun-Simmental AG, Department for Internal Medicine and Group of Medical Informatics, Thun, Switzerland

Summary

QUESTIONS UNDER STUDY: Drug-drug interactions (DDI) are considered a risk factor in medication safety and computerised alerting tools are increasingly promoted and implemented in order to detect and minimise DDI. As only little is known about the frequency and nature of DDI in hospitalised patients in Switzerland as well as about the usefulness of current alerting systems, this analysis based on a computerised medication record in a typical regional hospital setting was performed.

METHODS: All inpatients with at least one drug prescription between 2006 and 2010 were included. A total of 1,654,987 prescriptions were analysed with regard to the maximal seriousness level of DDI between each added prescription versus the existing prescription and with regard to all underlying DDI.

RESULTS: On average, each inpatient received 16 different drugs including on-demand prescriptions and encountered 5 DDI. A total of 27% of all prescriptions caused DDI. Within the last 12 months, 5% of all DDI were classified in category 1 (contraindicated), 3% in category 2, 53% in category 3, 8% in category 4 and 31% in category 5. The vast majority of DDI were caused by a very limited number of drugs.

DISCUSSION: Drug-drug interactions were very frequent and were very stable over the years studied, involving on average 27% of all prescriptions and 44% in internal medicine. Only a very limited amount of drugs were responsible for the vast majority of DDI, especially when the most severe categories of DDI were considered. Most of the severe DDI alerts could be automatically handled, if for example laboratory values could be taken into account. The DDI database should ideally be supplemented by information enabling more sophisticated computerised support in order to deliver more reasonable results from DDI checks.

Key words: *drug-drug interaction; Computerised Physician Order Entry CPOE; medication safety; adverse drug events*

Introduction

Drug-drug-interactions are considered a risk factor in medication safety and represent a relevant part of adverse drug events. As they are potentially preventable in many cases, and physicians and information systems designers are looking for strategies to detect, categorise and, consequently, prevent drug-drug-interactions (DDI). Adverse drug events (ADE) *per se* account for 19% of all adverse events [1], and 5–26% out of these are generated by DDI [2–4]. Due to multi-morbidity and polypharmacy, inpatients are especially prone to ADE [5]. A large university hospital based study detected DDI in 28% of all inpatients [6] and there seems to be an independent association between DDI and the length of stay, as well as the cost of a hospital stay [7]. Thus, handling DDI could enhance patient safety and reduce costs especially in the inpatient setting.

In recent years, efforts to increase patient safety with regard to the medication process have mainly focused on computerised physician order entry (CPOE). Within this area, decision support in terms of alerts (e.g., drug-allergy-alerts, drug-dosage-alerts, drug-drug interaction alerts DDI-A) increasingly controls or influences the prescription process of physicians. However, the value of DDI alerting is still very unclear as only limited data on the prevalence and incidence of DDI in certain countries exist, the clinical impact of drug interactions is often vague and – with current databases – only interactions between two single drugs can be tested.

Unfortunately, this usually leads to a huge gap between posted alerts (e.g., drug-drug-interaction alerts DDI-A) and alerts being accepted by physicians, therefore leading to compliance problems. A recent Dutch study, for example, showed that 91% of all drug related alerts were overridden by clinicians [8], and the overriding rate climbed to 98% when only DDI alerts were considered, questioning the sensibility of this support itself. Similar rates are reported elsewhere [9] with peer reviewers even attesting a 96%-correctness with regard to overruling. Therefore, DDI alerting does not seem to match everyday routine appropriately. Despite the fact that knowledge of underlying DDI is crucial when decision support is warranted, only little is known about the distribution of DDI in Switzerland. The DDI prevalence with regard to different departments or to specific drug pairs and differences between university and community based hospitals are particularly unknown. Furthermore, most studies have considered only small to medium sized patient samples, focused on specific patient

groups or used only trigger events for identifying potential DDI. In the most commonly used Swiss DDI database (GALDAT/HOSPINDEX), interactions are actually defined in a seriousness index consisting of six (until 2009 only five) categories (table 1).

The purpose of this study was twofold. The first purpose was to gain an overview of the frequency, nature and stability in time of DDI in a Swiss primary and secondary acute care hospital, and secondly, with respect to potential prevention strategies, to identify the most common single drugs creating the most serious interactions.

In the hospital sites studied, CPOE as part of the fully electronic patient record includes routine checks for DDI since 2004 and all data concerning prescriptions and drugs involved in DDI have been registered in parallel since the beginning. Representing the daily practice of a typical Swiss non-university hospital, this analysis included more than 10^6 prescriptions over a five year period.

The results could delineate current settings in Swiss hospitals concerning (preventable) adverse drug events and, furthermore, could enhance a critical appraisal of the DDI management especially in terms of decision support in electronic prescribing tools.

Materials and methods

The Spital STS AG is a publicly owned primary and secondary acute care regional hospital group with 310 inpatient beds distributed over three distant locations, caring for about 15,000 inpatients a year. As part of the fully electronic inpatient record, CPOE has been used since 2002 and has included routine checks for DDI since 2004. The DDI data are based on the official Swiss database GALDAT/HOSPINDEX™. Until 2009, this database defined five distinct categories of DDI seriousness, with category 1 being the most severe and category 5 being the least severe (table 1). In November 2009, an update and extension of the database was published, adding a sixth category and defining the five other categories in a more action-oriented manner, principally based on the propositions of Hansten et al. [10] and aligned with the German ABDA database.

With the CPOE system in use, adding new prescriptions to the medication record routinely starts a screening for DDI. The screening involves the whole medication record including the added drug(s), the current medication and all on-demand drugs and works without any user interruption. Two distinct pieces of information are stored during this process: the maximal DDI seriousness category (1–6) appearing during the prescription and all involved drugs identified by the specific drug code (pharmacode). The former information has primarily a screening character, whereas the latter can be used to test for all present drug interactions.

Additionally, available DDI checks (e.g., on-demand checks) do not influence the outlined data storage.

The current analysis included every prescription in all inpatients of the hospital group during the years 2006 to 2010. Medication records were included if at least one drug was prescribed. The incidence of the maximal seriousness category detected during the real-time DDI check was outlined for every year and additionally separated concerning the three distinct hospital clinics. Restricted to 2010 and the three most important categories, all drug pairs creating DDI are outlined. As newly added drugs are stored together with previously existing ones during the prescription process, cross checking these data can identify all drug pairs creating DDI. This analysis was performed retrospectively and results in more DDI than the check for the maximal level itself as more than one drug pair can create interactions of the same DDI category. As seriousness category four, five and six are clinically of little or no importance in general, only categories 1–3 are outlined in this analysis. 2010 was chosen due to the fact that it is a 12 month period following the introduction of the new classification database.

Results

On average, as shown in table 2, every inpatient stay results in 16 prescriptions of different drugs regardless of the department (13 prescriptions excluding on-demand drugs, data not shown in table 2). This figure remained quite steady over the years studied. The amount of prescribed drugs in relation to the different departments was steady as well, with the internal medicine department accounting for the highest amount (20) and the gynaecology/obstetrics department for the lowest (11). Every inpatient stay encountered 5 DDI on average.

Out of all prescriptions, 26–29% (2006–2010) created a DDI alert (DDI-A) independently of the DDI seriousness category (based on table 2). In internal medicine, 40–46% of all prescriptions created a DDI-A, compared to 20–24% in the surgical department and 6–8% in the gynaecology/obstetrics departments.

Between 2006 and 2009 and over all departments, the vast proportion of DDI-A (60–69%) corresponded to category 2. In these three years, category 2 and category 3 DDI-A accounted for 95% of all alerts. After the publication and immediate implementation of the revised DDI database in November 2009, a shift from category 2 interactions to category 5 interactions was noticed with a transition period in 2009. In 2010, the vast proportion of DDI-A corresponds to category 3 (51%) while 31% of DDI-A are due to the newly

Table 1
The seriousness classification used within the currently used Swiss drug-drug-interaction DDI database GALDAT. The number of categories as well as the distribution of DDI changed in November 2009 with a new category being implemented. As the changes occurred within the year of 2009, results in table 2 show a transition period in 2009.

DDI Classification	Category 1	Category 2	Category 3	Category 4	Category 5	Category 6
Previous classification (-2009)	Serious	Moderate	Weak	Insignificant	Occasional reports	
Current Classification (2009-)	Contraindicated	Probably contraindicated	Adjustments required	Adjustments probably necessary	Surveillance suggested	No measures required

defined category 5. Consequently, DDI-A in category 2 or category 3 were significantly less frequent in 2010 (56% vs 95%) compared to the previously used classification. The frequency of category 1 DDI-A was not affected by the change in the official database.

Table 3 shows the frequency of drugs creating alert categories one to three in 2010. Within a medication record, more than one drug pair can result in a given DDI category. Thus, all figures in table 3 show higher numbers than results in table 2. A total of 69% of all category 1 DDI were due to the potassium-spironolactone interaction, and an additional 22% were due to the interaction between potassium and parenteral nutrition products. The clopidogrel-esomeprazol interaction accounted for 13% of all category 2 DDI, the levodopa-metoclopramid DDI for 8% and the amiodarone-quetiapin DDI for 6%, whereas all other drug pairs did not exceed a 5% cut-off each.

Table 4 indicates the top ten drugs involved in DDI alerts of category one to three: the top three drugs in each category together accounted for 61% of all DDI in 2010 (41856 out of 68376 DDI, data not outlined in table 4).

Discussion

The frequency and nature of medication errors and adverse drug events in general have been widely studied in the last two decades [11–13]. Additional data indicate a prevalence of hospital admissions in adults or elderly patients due to or associated with ADE to be as much as 2–10% [2, 14–16]. Efforts to reduce errors in the medication process and thus to increase medication safety include the implementation and usage of CPOE systems. As adverse drug events are frequent and DDI are considered as relevant factors creating ADE, implementation of an alerting system for DDI and other preventable ADE has emerged over the years. As no internationally accepted and distributed classification system of DDI exists, many regions or countries have their own DDI databases in use. From experiences outside Switzerland, we can assume that the average number of alerts per admission is 4–8 [6], and that roughly 10 to 40% of all prescriptions in inpatients create DDI, independently of the seriousness category. In many cases, few drug combinations account for more than two thirds of all alerts. Furthermore, up to 50–70% of inpatients show DDI at admission or discharge [17–20].

Serious problems have been reported concerning physicians' compliance with alerts during the prescribing process. Emphasising this area of concern, van der Sijs et al. [8] reported a global overruling rate of 91% concerning alerts in the medication process and even a 98% overruling rate when DDI alerts were considered. However, system design and tiering of alerts to the clinical situation have the potential to increase compliance dramatically [21, 22].

In this study, all prescriptions performed in a five year period in a regional hospital setting were analysed with regard to DDI. On average, 16 different drugs were prescribed for every inpatient (13 if on-demand drugs were excluded). DDI were identified in 27% of all prescriptions. When broken down to distinct departments, clear differences could be seen between internal medicine (44%) and gynaecology (7%) for example, reflecting the very nature and the demography of patients in these specialities. These

Table 2
All cases with at least one drug prescription between 2006 and 2010 are indicated. The number of prescriptions and the number of drug-drug-interactions (DDI) are outlined as overall sum and as distribution within the DDI severity categories (until 2009 four categories with results, for the last two months of 2009 and for 2010 five categories with results). Category 6 (newly defined in 2009) has no DDI in the entire study period and thus the row is not outlined. The same figures are given for the three different clinics (internal medicine, surgery and orthopedics, gynaecology and obstetrics).
prescriptions (#/case): number of prescriptions and number of prescriptions per in-hospital stay

Year	#Cases	# prescriptions (#/case)	#DDI / #prescriptions (%)	# DDI(#/case)	Category 1 (%)	Category 2 (%)	Category 3 (%)	Category 4 (%)	Category 5 (%)
2006	11,682	187,794 (16)	26	49,537 (4)	2,890 (6)	32,681 (66)	11,159 (23)	2,807 (6)	0 (0)
2007	13,332	217,742 (16)	29	63,605 (5)	3,327 (5)	43,986 (69)	16,179 (25)	113 (0)	0 (0)
2008	13,235	211,897 (16)	27	57,605 (4)	3,157 (5)	34,448 (60)	19,903 (35)	97 (0)	0 (0)
2009	14,110	231,992 (16)	28	64,247 (5)	3,828 (6)	32,850 (51)	23,921 (37)	803 (1)	2,845 (4)
2010	15,170	258,450 (17)	26	68,376 (5)	3,559 (5)	2,200 (3)	36,039 (53)	5,315 (8)	21,263 (31)
Internal medicine									
2006	2,863	60,027 (21)	40	24,257 (8)	1,767 (7)	16,819 (69)	5,511 (23)	160 (1)	0 (0)
2007	3,314	67,979 (21)	46	31,224 (9)	1,881 (6)	21,252 (68)	8,027 (26)	64 (0)	0 (0)
2008	3,573	73,160 (20)	44	32,013 (9)	1,781 (5)	19,058 (60)	11,124 (35)	50 (0)	0 (0)
2009	3,885	79,218 (20)	45	35,385 (9)	2,327 (7)	18,988 (54)	12,427 (35)	165 (0)	1478 (4)
2010	4,459	88,362 (20)	43	37,592 (9)	1,839 (5)	1,518 (4)	22,542 (60)	745 (2)	10,948 (29)
Surgery /Orthopaedics									
2006	6,996	107,920 (15)	22	23,675 (3)	968 (4)	15,073 (64)	5,363 (22)	2,271 (10)	0 (0)
2007	8,021	127,941 (16)	24	31,006 (4)	1,399 (5)	21,696 (70)	7,862 (25)	49 (0)	0 (0)
2008	7,635	117,734 (15)	21	24,286 (3)	1,260 (5)	14,584 (60)	8,402 (35)	40 (0)	0 (0)
2009	8,064	129,772 (16)	21	27,359 (3)	1,462 (5)	13,252 (48)	10,852 (40)	523 (2)	1,270 (5)
2010	8,461	145,376 (17)	20	29,026 (3)	1,693 (6)	601 (2)	12,841 (44)	4,226 (15)	9,665 (33)
Gynaecology/Obstetrics									
2006	1,823	19,847 (11)	8	1,605 (1)	155 (10)	789 (49)	285 (18)	376 (23)	0 (0)
2007	1,997	21,822 (11)	6	1,375 (1)	47 (3)	1,038 (75)	290 (20)	0 (0)	0 (0)
2008	2,027	21,003 (10)	6	1,306 (1)	116 (9)	806 (62)	377 (29)	7 (1)	0 (0)
2009	2,161	23,002 (11)	7	1,503 (1)	39 (3)	610 (41)	642 (43)	115 (8)	97 (6)
2010	2,250	24,712 (11)	7	1,758 (1)	27 (2)	81 (5)	656 (37)	344 (20)	650 (37)

results were very stable over the years and well in line with previous results in other countries although the classification system is different. Due to changes in the DDI database, a shift from category 2 to a newly created category 5 could be noticed in 2009.

Within the most relevant seriousness category, the majority of registered DDI (and therefore most of the alerts being presented to the prescribers in a disruptive manner) were due to the interaction between potassium and potassium-sparing agents, primarily spironolactone. Although hyperkalemia can be life threatening, many patients in need for this combination will in fact have a hypokalemia and will suffer from chronic heart failure for example. Therefore, the effect of the combination therapy is likely to be intended rather than unintentional. Furthermore, potassium levels are likely to be under strict control in an inpatient setting. The same situation might be present in the second most frequent DDI with the highest seriousness level, the interaction between potassium and parenteral nutrition. These two DDI alone accounted for 90% of all category 1 interactions and have major implications for the prescriber, as the most dangerous DDI are usually presented in an interruptive manner. In category 2 DDI, only the interaction clopidogrel/esomeprazol and levodopa/metoclopramid exceeded a 10% cut-off. In category 3, phenprocoumon, metoprolol, prednison and acetylsalicate were the only drugs accounting for more than 5% of all DDI-A.

These results lead to several key messages. Firstly, the frequency as well as the nature of DDI show a high stability over years and a huge impact of a very limited number of drugs on the overall DDI alert rates, especially in the two most important seriousness categories. Secondly, a discrepancy between the most frequent DDI and their clinical significance concerning the individual patient has to be

Table 3

The frequency and nature of drug-drug-interactions (DDI) in 2010 over all clinics, separated in severity categories 1, 2 and 3. As more than one drug pair can result in a same DDI category alert within a given prescription, the number of drug pairs exceeds the number of DDI outlined in table 2. In category two and three, only the top ten drug pairs are indicated.

In category one, four drug-pairs account for 97% of all DDI. In category two and three, the top ten DDI account for 52% and 57% of all DDI respectively. For category 3, due to the huge amount of different drugs used, class effects are taken together, where appropriate (e.g., angiotensin-converting enzyme inhibitors ACE).

+Each single DDI not specifically outlined (others, number of specific DDI in brackets indicated) accounts for less than 2% of all DDI.

*Nutriflex is a commercially available, parenteral nutrition solution (ATC B05BA10).

ACE: angiotensin-converting enzyme inhibitor

ARB: angiontensin-receptor blocking agent

NSAID: non-steroidal anti-inflammatory agent

Category 1 DDI	**Frequency of DDI (%)**
Potassium-spironolacton	2,894 (69)
Spironolacton-nutriflex*	936 (22)
Ceftriaxon-nutriflex*	146 (3)
Atorvastatin-clarithromycin	117 (3)
Others+ (11)	117 (3)
Total	4,210 (100)
Category 2 DDI	
Clopidogrel-esomeprazol	374 (13)
Levodopamin-metoclopramid	239 (8)
Amiodarone-quetiapin	171 (6)
Amiodarone-trimipramin	147 (5)
Clopidogrel-ciprofloxacin	142 (5)
Amiodarone-haloperidol	119 (4)
Amiodarone-clarithromycin	81 (3)
Rifamycine-atovaqone	74 (3)
Amiodarone-risperidon	59 (2)
Clarithromycin-salmeterol	57 (2)
Others+ (74)	1,420 (48)
total	2,883 (100)
Category 3 DDI	
Betablocker-betamimetics	8,856 (11)
Spironolactone-ACE-inhibotors/ARB	7,661 (10)
Acetylsalicalate-enoxaparine	4,891 (6)
Betablocker-insulin	4,260 (5)
Acetylsalicalate-prednisone	3,473 (4)
Prednisone-insulin	2,977 (4)
Digoxin-diuretics	2,741 (3)
Calcium/cholecalciferol-thiaciddiuretics	2,501 (3)
Amiodaron-betablocker	2,133 (3)
Phenprocoumon-atorvastatin	1,885 (2)
Prednison- NSAID	1,828 (2)
Acetylsalicalate-clopidogrel	1,515 (2)
Others+ (112)	34,098 (43)
Total	78,819 (199)

discussed. Thirdly, the vast majority of alerts could be prevented by taking into account the current clinical context, for example laboratory values like potassium levels. By doing this, up to 90% of category 1 DDI could potentially be suppressed, leading to far less alerts for the prescribers and most probably to a less intense alert fatigue and thus an increased compliance with DDI alerts. Fourth, some DDI are stated although they only affect a certain patient category (e.g., DDI between parenteral nutrition and ceftriaxon, being only relevant in children). Fifth, there seems to be a gap between the appearance of DDI as defined in the official database and the clinical expertise, where for example DDI involving anticoagulation treatment, drug levels or drug resorption problems due to chelation are often cited as a major concern. Additionally, the implication of many DDI is discussed controversially like the clopidogrel-esomeprazol interaction for example.

The strength of this study is the inclusion of all prescriptions in a period of five consecutive years. Due to CPOE and the chosen implementation, a complete workup of prescriptions was possible, making unwarranted influences by individual physicians, short term trends in pharmacotherapy or dependency of manually performed DDI checks very unlikely. Due to this, the outlined data are very representative for other Swiss hospitals in this setting. Furthermore, drugs on an as-needed basis can be included as well, reflecting a safety issue during drug administration.

The study has some limitations as well. Firstly, inclusion of on-demand prescription might show a certain correlation to existing order sets (e.g., metoclopramid on a on-demand basis for nausea). As on-demand orders are included as well, the overall quantity of DDI could be overestimated with regard to permanent orders. However, it is a fact that on demand drugs could be used anytime and DDI-A should take this into account. Secondly, as the prescribing process initiates automatic DDI checking, ordering single drugs instead of multiple drugs in the same prescribing process could theoretically lead to an increase of DDI alerts, as the trigger event for DDI checking is the transcription of added drugs to the existing medication administration record. However, this overestimation should not affect the distribution within the drugs but only the overall amount of DDI.

Independently of the current study design it has to be kept in mind that current checks for DDI can only handle single drug pairs. Knowledge about DDI in more than two involved drugs is scarce and corresponding databases are even absent. Thus, current analysis of polypharmacy is reduced to DDI between two specific drugs.

Facing the results of the current analysis, we can assume that the current Swiss DDI database should be supplemented by structured, drug specific data on affected patient groups (e.g., adults, children), clinical relevance (e.g., in contrast to *in vitro* relevance), clinical evidence for the outlined DDI and, most of all, strategies concerning alert handling (e.g., laboratory values including cut-offs). This additional information could enhance critical appraisal with regard to DDI and enable system designers to cope with DDI alerts in a differentiated manner. By doing this,

Table 4
The most frequent drugs involved in DDI alerts within the DDI categories 1–3 and during 2010 are outlined. In category 1, drugs creating more than 50 DDI-A are indicated. In category 2 and 3 only the top ten drugs are indicated.

Category 1 DDI	**Drug involved in DDI (%)**
Spironolactone	3,830 (45)
Potassium	2,894 (34)
Nutriflex	1,082 (13)
Ceftriaxon	146 (2)
Atorvastatin	117 (1)
Clarithromycine	117 (1)
Category 2 DDI	
Clopidogrel	1,457 (25)
Esomeprazol	1,329 (23)
Amiodarone	575 (10)
Metoclopramid	251 (4)
Levodopa/benserazide	248 (4)
Ciprofloxacin	182 (3)
Quetiapin	177 (3)
Clarithromycine	144 (2)
Trimipramine	147 (3)
Haloperidol	119 (2)
Category 3 DDI	
Phenprocoumon	10,711 (7)
Metoprolol	10,089 (6)
Prednison	9,889 (6)
Acetylsalicylate	7,980 (5)
Salbutamol	5,105 (3)
Amiodaron	4,950 (3)
Calcium/cholcalciferol	4,361 (3)
Atorvastatin	3,879 (2)
Enoxaparine	3,851 (2)
Lisinopril	3,228 (2)

reasonable support concerning DDI could be implemented in current CPOE systems. Otherwise, as outlined by previous studies, most DDI alerts will be overridden due to the bad match between prescribed drugs and the relevance of the alert facing the clinical situation. Overriding rates of more than 90% and, furthermore, the fact that overriding seems to be appropriate clearly indicates over-alerting, and increases not only alert fatigue but also the chance of missing relevant DDI due to lowered overall attention.

CPOE has shown considerable potential to improve prescribing quality and patient safety, given a professional and seamless integration into clinical workflows. Adding decision support in terms of DDI checking however – although technically simple – is a challenging task facing the existing database and the multifaceted clinical settings. Efforts have to be undertaken to cope with the existing data in order to minimise noise by unnecessary alerting and further supplement available pharmacological database in order to deliver a reasonable basis for further decision support.

Funding / potential competing interests: No financial support and no other potential conflict of interest relevant to this article were reported.

Correspondence: *Marc Oertle, MD MSc, Leitender Arzt Medizin & MedizinInformatik, Krankenhausstrasse 12, CH-3600 Thun, Switzerland, marc.oertle[at]spitalstsag.ch*

References

1 Brennan TA, Leape LL, Laird NM, Hebert L, Localio AR, Lawthers AG, et al. Incidence of adverse events and negligence in hospitalized patients. Results of the Harvard Medical Practice Study I. N Engl J Med. 1991;325(3):210.

2 Leape LL, Bates DW, Cullen DJ, Cooper J, Demonaco HJ, Gallivan T, et al. Systems analysis of adverse drug events. ADE Prevention Study Group. JAMA. 1995;274(1):35–43.

3 Hug BL, Witkowski DJ, Sox CM, Keohane CA, Seger DL, Yoon C, et al. Adverse drug event rates in six community hospitals and the potential impact of computerized physician order entry for prevention. J Gen Intern Med. 2010;25(1):31–8.

4 McDonnell PJ, Jacobs MR. Hospital admissions resulting from preventable adverse drug reactions. Ann Pharmacother. 2002;36(9):1331–6.

5 Sanchez Munoz-Torrero JF, Barquilla P, Velasco R, Fernandez Capitan Mdel C, Pacheco N. Adverse drug reactions in internal medicine units and associated risk factors. Eur J Clin Pharmacol. 2010;66(12):1257–64.

6 Zwart-van Rijkom JE, Uijtendaal EV, ten Berg MJ, van Solinge WW, Egberts AC. Frequency and nature of drug-drug interactions in a Dutch university hospital. Br J Clin Pharmacol. 2010;70(4):619–20.

7 Moura CS, Acurcio FA, Belo NO. Drug-drug interactions associated with length of stay and cost of hospitalization. J Pharm Pharm Sci. 2009;12(3):266–72.

8 van der Sijs H, Mulder A, van Gelder T, Aarts J, Berg M, Vulto A. Drug safety alert generation and overriding in a large Dutch university medical centre. Pharmacoepidemiol Drug Saf. 2009;18(10):941–7.

9 Weingart SN, Toth M, Sands DZ, Aronson MD, Davis RB, Phillips RS. Physicians' decisions to override computerized drug alerts in primary care. Arch Intern Med. 2003;163(21):2625–31.

10 Hansten PD, Horn JR, Hazlet TK. ORCA: OpeRational ClassificAtion of drug interactions. J Am Pharm Assoc (Wash). 2001;41(2):161–5.

11 Leape LL, Brennan TA, Laird N, Lawthers AG, Localio AR, Barnes BA, et al. The nature of adverse events in hospitalized patients. Results of the Harvard Medical Practice Study II. N Engl J Med. 1991;324(6):377–84.

12 Morimoto T, Gandhi TK, Seger AC, Hsieh TC, Bates DW. Adverse drug events and medication errors: detection and classification methods. Qual Saf Health Care. 2004;13(4):306–14.

13 Jylha V, Saranto K, Bates DW. Preventable adverse drug events and their causes and contributing factors: the analysis of register data. Int J Qual Health Care. 2011;23(2):187–97.

14 Kongkaew C, Noyce PR, Ashcroft D. Hospital admissions associated with adverse drug reactions: a systematic review of prospective observational studies. Ann Pharmacother. 2008;42(7):1017–25.

15 Bates DW, Cullen DJ, Laird N, Petersen LA, Small SD, Servi D, et al. Incidence of adverse drug events and potential adverse drug events. Implications for prevention. ADE Prevention Study Group. JAMA. 1995;274(1):29–34.

16 Fijn R, Van den Bemt PM, Chow M, De Blaey CJ, De Jong-Van den Berg LT, Brouwers JR. Hospital prescribing errors: epidemiological assessment of predictors. Br J Clin Pharmacol. 2002;53(3):326–31.

17 Fokter N, Mozina M, Brvar M. Potential drug-drug interactions and admissions due to drug-drug interactions in patients treated in medical departments. Wien Klin Wochenschr. 2010;122(3–4):62–4.

18 Vonbach P, Dubied A, Krahenbuhl S, Beer JH. Prevalence of drug-drug interactions at hospital entry and during hospital stay of patients in internal medicine. Eur J Intern Med. 2008;19(6):413–20.

19 Egger SS, Drewe J, Schlienger RG. Potential drug-drug interactions in the medication of medical patients at hospital discharge. Eur J Clin Pharmacol. 2003;58(11):773–8.

20 Bertoli R, Bissig M, Caronzolo D, Odorico M, Pons M, Bernasconi E. Assessment of potential drug-drug interactions at hospital discharge. Swiss Med Wkly. 2010;140:w13043.

21 Paterno MD, Maviglia SM, Gorman PN, Seger DL, Yoshida E, Seger AC, et al. Tiering drug-drug interaction alerts by severity increases compliance rates. J Am Med Inform Assoc. 2009;16(1):40–6.

22 Bonnabry P, Despont-Gros C, Grauser D, Casez P, Despond M, Pugin D, et al. A risk analysis method to evaluate the impact of a computerized provider order entry system on patient safety. J Am Med Inform Assoc. 2008;15(4):453–60.