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DOI:
10.1016/j.ijmedinf.2017.12.027

Document Version
Peer reviewed version

Citation for published version (Harvard):
Cornu, P, Phansalkar, S, Seger, DL, Cho, I, Pontefract, S, Robertson, A, Bates, DW & Slight, SP 2018, 'High-priority and low-priority drug-drug interactions in different international Electronic Health Record systems: a comparative study', *International Journal of Medical Informatics*, vol. 111, pp. 165-171. https://doi.org/10.1016/j.ijmedinf.2017.12.027

Submission to the International Journal of Medical Informatics

High-priority and low-priority drug-drug interactions in different international Electronic Health Record systems: a comparative study

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Key Words: clinical decision support systems; drug interactions; hospital; electronic health records; high-risk medicines

Word count main text: 3,351

Word count abstract: 247

Number of tables: 6

ABSTRACT

Objectives: To investigate whether alert warnings for high-priority and low-priority drug-drug interactions (DDIs) were present in five international electronic health record (EHR) systems, to compare and contrast the severity level assigned to them, and to establish the proportion of alerts that were overridden.

Methods: We conducted a comparative, retrospective, multinational study using a convenience sample of 5 EHRs from the U.S., U.K., Republic of Korea and Belgium.

Results: Of the 15 previously defined, high-priority, class-based DDIs, alert warnings were found to exist for 11 in both the Korean and UK systems, 9 in the Belgian system, and all 15 in the two US systems. The specific combinations that were included in these class-based DDIs varied considerably in number, type and level of severity amongst systems. Alerts were only active for 8.4% (52/619) and 52.4% (111/212) of the specific drug-drug combinations contained in the Belgian and UK systems, respectively. Hard stops (not possible to override) existed in the US and UK systems only. The override rates for high-priority alerts requiring provider action ranged from 56.7 % to 83.3%. Of the 33 previously defined low-priority DDIs, active alerts existed only in the US systems, for three class-based DDIs. The majority were non-interruptive.

Conclusions: Alert warnings existed for most of the high-priority DDIs in the different EHRs but overriding them was easy in most of the systems. In addition to validating the high- and low-priority DDIs, this study reported a lack of standardization in DDI levels across different international knowledge bases.

BACKGROUND AND SIGNIFICANCE

Drug–drug interactions (DDIs) occur frequently and pose a threat to patient safety. [1] Medication related clinical decision support (CDS) systems have been integrated into electronic health record (EHR) systems worldwide and can alert physicians to potentially dangerous DDIs during the prescribing process.[2-6] However, CDS systems can also generate alerts with low specificity, resulting in high override rates and alert fatigue amongst prescribers.[5] Several studies reported alert override rates in excess of 80%, even for those DDIs that have the potential to cause severe patient harm.[7-11]

Tiering of DDI alerts by severity represents one strategy for improving DDI alert specificity.[12] Put simply, DDIs can be categorized into groups and presented to prescribers in different ways (interruptive or non-interruptive) depending on the group to which they belong.[12] In an attempt to guide this process, Phansalkar et al. identified a minimum starter set of 15 clinically significant DDIs that should always be categorized as 'high severity' and generate warnings in all EHRs.[13] Phansalkar et al. also identified 'low-priority' DDIs, 33 of which did not warrant interruptive alerting.[14] These lists have served as a good starting point for tiering alerts in EHR systems, although they represent extremes. The implementation of the high priority DDIs list was recently investigated by McEvoy and colleagues in EHRs across the United States but this has not been evaluated internationally.[15] The implementation of the low-priority DDI list has also not been evaluated. To provide insight in DDI alerting practices in different countries, we investigated whether alert warnings for the 15 high-priority and 33 low-priority DDIs existed in five different international EHRs, compared and contrasted the severity level assigned to them, and establish the proportion of overridden alerts.

MATERIALS AND METHODS

Design

We conducted a comparative, retrospective, multinational study in four countries: U.S., U.K., Republic of Korea and Belgium. Alert warnings and DDI knowledge base content for the 15 high-priority [13] and 33 low-priority DDIs [14] were compared between different EHR systems implemented at Partners Healthcare (Boston, USA), University Hospitals Birmingham NHS Foundation Trust (Birmingham, UK), Universitair Ziekenhuis Brussel (Brussels, Belgium), and Asan Medical Center (Seoul, Korea). All five EHRs were built in-house and used medication knowledge bases that were created in-house with the exception of the Belgian EHR. Alert data were downloaded from each of the four international study sites between 1st January 2009 and 31st December 2011, with two exceptions. Although data from the Partners Healthcare outpatient system was available for the requested time period, data from the inpatient system was only available from 1st January 2012 to 31st December 2012 (after tiered alerting was implemented). Data from the Asan Medical Center was limited to three consecutive months from 1st February 2012 to 31st April 2012.

Description of EHRs at International Study Sites

Partners HealthCare, U.S.

Partners HealthCare is a regional integrated healthcare delivery system located in the North East of the U.S. Prior to 2015, physicians working in the ambulatory setting used a self-developed, Certification Commission for Healthcare Information Technology (CCHIT)-approved, EHR system called the Longitudinal Medical Record (LMR). For over 20 years (1984-2015), physicians working at the 777-bed, Brigham and Women's teaching hospital used the Brigham

Integrated Computing System (BICS) to place all medication and laboratory orders. BICS provided a range of different types of CDS alerts, including DDIs that were tiered: Level 1 alerts were hard stops (not possible to override), level 2 alerts were interruptive and required provider action (possible to override), and level 3 alerts were non-interruptive (information only).

University Hospitals Birmingham NHS Foundation Trust, U.K.

The University Hospital Birmingham NHS Foundation Trust (UHBFT) is a large acute NHS teaching hospital in the UK. It has approximately 1,200 inpatient beds and provides care to patients across a range of medical and surgical specialties, with the exception of pediatrics, obstetrics and mental health. Since 2004, UHBFT used a locally developed system called PICS (Prescribing, Information and Communication System) for the prescribing and administration of all inpatient and discharge prescriptions, with the exception of some anti-cancer treatments. PICS presented CDS alerts in one of three ways: (1) hard stop that prevents an action within the system (Level 1); (2) override alert requiring a *password* to continue (Level 2); (3) system warning or information requiring an *acknowledgment* to continue (Level 3).

UZ Brussel, Belgium

The UZ Brussel is a 721-bed university hospital in Brussels, Belgium. The hospital system includes CDS functionality for drug prescribing, with a user interface that was developed in-house.[16-19] DDI screening was gradually implemented across all hospital departments in 2009. During the study period, only interruptive DDI alerts were triggered at the point of prescribing. These alerts did not require the healthcare provider to give an override reason in order to continue but did require the order to be reconfirmed before sending it to pharmacy. The commercially

available DelphiCare® knowledge base supported DDI checking, with DDIs categorized in to six levels depending on their severity and likelihood of occurrence (Table 1).[4, 20]

Table 1: Severity and likelihood of occurrence classification in DelphiCare®

DelphiCare® Severity classification prior to October 2013 [20]	
1	Contraindicated
2	Precautionary contraindicated
3	Monitoring or therapy adjustment needed
4	In some cases monitoring or therapy adjustment is needed
5	Precautionary monitoring
6	No action needed
DelphiCare® Likelihood of occurrence classification [20]	
Reported	Evidence for occurrence is reported in the literature
Expected	It may be expected that the interaction will occur
Not known	Not possible to make a statement
Unlikely	It is unlikely that the interaction will occur

The system was set up to trigger interruptive alerts only for DDIs that were considered contraindicated (Level 1) or precautionary contraindicated (Level 2). These alerts were displayed in the same way to the user with the respective level indicated.[4] DelphiCare® also assigned a 'likelihood of occurrence' level to the DDIs (reported, expected, not known, unlikely) as shown in Table 1. During the study period, the CDS system at UZ Brussels was only set up to trigger alerts for those DDIs classified as 'Reported'. However, for the purposes of this study, we downloaded data on all DDI alerts that had either a 'Reported' or 'Expected' likelihood of occurrence level across all severity levels.

Asan Medical Center, South Korea

The Asan Medical Center is a tertiary teaching hospital with 2,000 beds located in Seoul, South Korea. It has home-grown EHR system, which is used throughout the hospital by all physicians working in both inpatient and outpatient departments. The hospital introduced interruptive DDI

alerts in 2012 at the same time as other types of alerts e.g., drug allergy, duplication, pregnancy contraindication, and drug formulary. These DDI rules consisted of 476 drug pairs, comprising of 77 drug classes and 238 drugs. They were developed nationally based on the product labeling information provided by the Korea Food and Drug Administration, and their implementation enforced by the Health Insurance Review Agency (HIRA) in all ambulatory and outpatient settings throughout the country.

Data collection

Data were downloaded from the alert log database in each of the five international systems and patient identifiers removed. The necessary approvals were obtained from each organizations' respective ethics committee or institutional review boards e.g., UZ Brussel Medical Ethics Committee (Belgium), Partners Human Research Committee (US),
UHBFT Research and Development Department (UK), and Asan Medical Center Institutional Review Board (Korea).

Statistical analysis

Descriptive analyses were used to summarize the types and number of DDI alerts, the override rates, and the number of prescriptions with a DDI. Descriptive analyses were carried out with Microsoft® Excel® 2010 (Microsoft Corp, Redmond, WA).

RESULTS

High-priority, class-based DDIs

(1) What 'high-priority' class-based DDI alert warnings existed in each of the five international systems and what severity levels were assigned to them?

Of 15 previously defined, high-priority, class-based DDIs,[13] alert warnings were found to exist for all in the two US systems, 11 in both the Korean and the UK systems, and 9 in the Belgian system. The ramelteon and CYP1A2 inhibitors interaction was not included in the UK and Korean systems. The Korean system also did not have alert warnings for neither the febuxostat and azathioprine/mercaptopurine, nor the strong CYP3A4 inducers and protease inhibitors class-based DDIs (e.g. Rifampin-Atazanavir). In the UK system, the irinotecan and strong CYP3A4 inhibitors interaction, and the tizanidine and strong CYP1A2 inhibitors interaction were not included. The tranylcypromine and procarbazine interaction was only included in the two US systems.

The severity level assigned to the class-based DDIs varied extensively between international systems (Table 2). Hard stops existed for 11 class-based DDIs in the US inpatient system, 12 class-based DDIs in the US outpatient system, and 5 class-based DDIs in the UK system. There were no hard stops in the Belgian or Korean systems. Interruptive alerts requiring provider action (possible to override) existed for 11 class-based DDIs in the Korean system, 10 class-based DDIs in the US systems, 9 class-based DDIs in the Belgian system and 8 class-based DDIs in the UK system.

Table 2: Overview of the 15 'high-priority' class-based DDIs and the assigned severity levels in each of the different international EHR systems

Object class name	**Precipitant class name**	**UZ Brussel[a, b] (Level 1 to 6)**	**US BICS inpatient[b, c] (Level 1 to 3)**	**US LMR outpatient (Level 1 to 3)[b]**	**AMS Korea[c] (Level 2 only)**	**PICS, UK (Level 1 to 3)[b]**
Amphetamine and Derivatives	MAO inhibitors	1[a]	1 & 2	1 & 2	2	2
Atazanavir	Proton pump inhibitors	2[a]	2	1 & 2	2	1
Febuxostat	Azathioprine /mercaptopurine	3	1	1	n/a	2
SSRIs	MAO inhibitors	1[a]	2	1 & 2	2	1 & 2
Irinotecan	Strong CYP3A4 inhibitors	3 & 5	1	1	2	n/a
Narcotic analgesics	MAO inhibitors	2[a]	1 & 2	2	2	2
Tricyclic antidepressants	MAO inhibitors	3	1	1	2	2
QT prolonging agents	QT prolonging agents	1[a], 2[a], 3 & 5	1,2 &3	1, 2 & 3	2	1, 2 & 3
Ramelteon	CYP1A2 inhibitors	2 & 3	1	1	n/a	n/a
Strong CYP3A4 inducers	Protease inhibitors	1[a], 2[a], 3 & 5	2 & 3	2 & 3	n/a	2
HMG Co-A reductase inhibitors	CYP3A4 inhibitors	1[a] & 3	1,2&3	1, 2 & 3	2	1 & 2
CYP3A4 inhibitors	Ergot alkaloids and derivates	1[a] & 2	2	2	2	1
Tizanidine	CYP1A2 inhibitors	1[a] & 3	1,2,&3	1, 2 & 3	2	n/a
Tranylcypromine	Procarbazine	n/a	1	1	n/a	n/a
Triptans	MAO inhibitors	2	1 & 2	1 & 2	2	1

[a] Alert warnings were included in the Belgian database for 14 class-based alerts but the system was activated for only 9 class-based alerts.
[b] The level of decision support varied according to the drug selected in a class.
[c] Data from 2012 for the US Inpatient system, from February 1 to April 31 for the Korean system and from 2009 till 2011 for all other systems.

(2) How many individual drug-drug combinations were included in these 'high-priority' class-based DDIs and how did their severity level vary both within and between different systems?

There were 742 individual drug-drug combinations included in the 15 class-based DDIs listed in the original high-priority DDI paper.[13] Of these, 619 (83.4%) were included in the Belgian system, 462 (62.3%) in the BICS system, 441 (59.4%) in the LMR system, 212 (28.6%) in the UK system and 53 (7.1%) in the Korean system. For the US and Korean systems, alerts were active for all individual drug-drug combinations. However, in the Belgian and UK systems, alerts were only active for 8.4% (52/619) and 52.4% (111/212) of the specific drug-drug combinations, respectively (Table 4). The specific drug-drug combinations that were included in the class-based interactions also varied considerably both in the type and severity level between the different EHRs. For example, of the 23 strong CYP3A4 inhibitors that could interact with irinotecan, only five (aprepitant, fluconazole, itraconazole, ketoconazole and voriconazole) were included in the Belgian system, one (ketoconazole) in both US systems, one (atazanavir) in the Korean system, and none in the UK system. Furthermore, the individual drug-drug combination *quinidine and methadone* in the class-based DDI of QT prolonging agents & QT prolonging agents was assigned a severity level 1 (contraindicated) in the Belgian system, whereas *quinidine and chloroquine* in the same class-based DDI was assigned a level 5 (patient follow up) in the same system. These combinations were both assigned a severity level 2 in the US systems and were not included in the Korean and UK systems (Table 3). Finally, the severity level also changed for some of these specific drug-drug combinations during the study period e.g., the simvastatin and CYP3A4 inhibitors combinations (ketoconazole) level changed from a level 3 (2009 – 2010) to a level 2 (2010 – 2011) and finally to a level 1 (2011 - onwards) in the US outpatient system.

Table 3: Examples of individual drug-drug combinations that varied across three or more levels in the five international EHR systems

DDI pair	UZ Brussel[a] (Level 1 to 6)	US BICS inpatient (Level 1 to 3)	US LMR outpatient (Level 1 to 3)	AMS Korea[b] (Level 2 only)	PICS, UK (Level 1 to 3)
#6. Febuxostat-azathioprine/ Mercaptopurine	3	1	1	Not included	2
#20. Tricyclic antidepressants-MAO inhibitors	3	1	1	2	2
Amitriptyline-Selegiline	3	1	1	2	2
Doxepin-Phenelzine	3	Not included	Not included	Not included	2
Dosulepin-Procarbazine	3	Not included	Not included	Not included	2
#21. QT prolonging agents-QT prolonging agents	1, 2, 3 & 5	1, 2 & 3	1, 2 & 3	2	Variable
Quinidine-Methadone	1	2	2	Not included	Not included
Amiodarone-Chloroquine	5	2	2	Not included	1
Disopyramide-Chlorpromazine	2	3	3	Not included	2
Quinidine-Chloroquine	5	2	2	Not included	Not included
#23. Strong CYP3A4 inducers - Protease inhibitors	1, 2, 3 & 5	2 & 3	2 & 3	Not included	2
Bosentan-Ritonavir	5	2	2	Not included	2
Rifampin-Atazanavir	1	3	3	Not included	2
Rifabutin-Indinavir	3	3	3	Not included	2
#25. HMG Co-A reductase inhibitors- CYP3A4 inhibitors	1 & 3	1, 2 & 3	1, 2 & 3	2	Variable
Lovastatin-Erythromycin	1	1 & 3[a]	3	2	Not included
Simvastatin-Ketoconazole	1	1	1, 2 & 3[a]	2	Not included
Simvastatin-Itraconazole	1	1	2 & 3[a]	2	2
Simvastatin-Clarithromycin	1	1	1, 2 & 3[a]	2	Not included
Simvastatin-Ritonavir	3	1	1 & 2[a]	2	1

[a] The alert level for the specific drug-drug combination changed during the study period

(3) How many 'high-priority' DDI alert warnings were triggered to users of each of the different international EHR systems and how often were these overridden?

During the study period, 76 (1.8%) hard stop alerts were generated in the US inpatient system, 768 (4.4%) in the US outpatient system, and 20 (52.6%) in the UK system. There were no hard stop alerts displayed in the Belgian and Korean systems, but the number of interruptive alerts generated that required provider action was 215 (100%) and 43 (100%) in the Belgian and Korean systems, respectively. The override rate for the interruptive alerts was lower in the US outpatient system (56.7%) than in all other systems (74.9 – 83.3%, Table 4). The high override rates were concentrated in a few

class-based DDIs. In the Belgian, US inpatient, US outpatient and Korean system respectively 93.2%, 70.9%, 96.2% and 81.8% of the overridden alerts were part of the HMG Co-A reductase inhibitors and CYP3A4 inhibitors interaction. Additionally, 28.9% and 3.4% of the overrides in the US inpatient and outpatient system respectively were located in the QT prolonging agents & QT prolonging agents interaction. In the UK system, 73.3% of the overridden alerts were part of the narcotic analgesics and MAO inhibitors interaction.

Table 4: An overview of the interruptive/non-interruptive nature of the high priority class-based DDIs and the total number of alerts triggered in the five international EHRs

		UZ Brussel	*US BICS Inpatient*[c]	*US LMR Outpatient*	*AMS Korea*[c]	*PICS, UK*
Class-based alerts included		**9** (14[a])	**15**	**15**	**11**	**11**
Interruptive alerts (class-based)	Hard stops	-	11[b]	12[b]	-	5[b]
	Provider action required	9	10[b]	10[b]	11	8[b]
Non-interruptive/informational alerts (class-based)		-	4[b]	4[b]	-	-
Individual combinations included		**52 (619[a])**	**462**	**441**	**53**	**111 (212[d])**
Interruptive alerts	Hard stops	-	89	92	-	38
	Provider action required	52	304	267	53	73
Non-interruptive/informational alerts		-	69	82	-	-
Total alerts fired		**215** (3648[a])	**4302**	**17489**	**43**	**38**
Interruptive alerts	Hard stops	-	76	768	-	20
	Provider action required	215	3740	6873	43	18
	Override rate (%)	74.9%	80.2%	56.7%	76.7%	83.3%
Total non-interruptive alerts fired		-	486	9848	-	-

[a] Alert warnings were included in the database for 14 class-based alerts (619 combinations) but the system was activated for only 9 class-based alerts (52 combinations). Only 215 alerts were generated while 3,648 could have been triggered.

[b] Different classification levels were assigned to specific combinations within the same class-based interaction or levels changed during study period

[c] Data from 2012 for the US Inpatient system, from February 1 to April 31 for the Korean system and from 2009 till 2011 for all other systems

[d] Alert warnings were included in the database for 212 combinations but the system was activated for only 111 combinations

Non-interruptive/informational alerts existed only in the US systems for 4 class-based DDIs and accounted for 11.3%, and 56.3% of the alerts displayed in the US inpatient and US outpatient systems, respectively.

Low-priority, class-based DDIs

4) *What 'low-priority' class-based DDI alert warnings existed in each of the five international systems and what severity levels were assigned to them?*

The UK and Korean system alerted on none of the 33 low-priority class-based DDIs that could safely remain 'non-interruptive' in the original list.[14] The Belgian system included 24 low-priority class-based DDIs in the database but alerts were not active for any of these (53,437 alerts could have been triggered). Most of these class-based DDIs were assigned level 5 (precautionary monitoring), although there were eight assigned a severity level of 3 (monitoring or therapy adjustment needed), and one assigned a severity level of 2 (precautionary contraindicated). Three low-priority, class-based DDIs were included in the US systems and assigned a severity Level 2 or 3 (e.g., niacin and statins; proton pump inhibitors and imidazoles; anticoagulants and statins). Table 5 provides an overview of the 33 low-priority class-based DDIs and the level of severity assigned to them in the Belgian and US systems.

Table 5: Overview of 33 low-priority class-based DDIs and level of severity of alerts in the Belgian and US systems.

Object class name	**Precipitant class name**	**Level Belg.**	**Nr. of prescr. Belg.**	**Alerts Belg.[a]**	**Level US inpatient[b]**	**Alerts US inpatient**	**Level US outpatient**	**Alerts US outpatient**
ACE inhibitors	Salicylates	4	750	n/a	n/a	n/a	n/a	n/a
Niacin	Statins	5	0	n/a	2 & 3	29 (2) 447 (3)	2 & 3	215 (2) 9683 (3)
β-adrenergic blockers	Serotonin reuptake blockers	2 & 5	335	n/a	n/a	n/a	n/a	n/a
Iron salts	Proton pump inhibitors	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Thiazide-type diuretics	ACE inhibitors	5	3361	n/a	n/a	n/a	n/a	n/a
Thyroid hormones	Calcium salts	3	942	n/a	n/a	n/a	n/a	n/a
Thyroid hormones	Statins	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Thiazide-type diuretics	NSAIDS	4	1642	n/a	n/a	n/a	n/a	n/a
β-adrenergic blockers	Thyroid hormones	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Macrolide immunosuppressives	Corticosteroids	5	1280	n/a	n/a	n/a	n/a	n/a
Antacids	Corticosteroids (oral)	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Bisphosphonates	Calcium salts	3	700	n/a	n/a	n/a	n/a	n/a
Vitamin B12	Omeprazole	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Folic Acid	Methotrexate	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Sulfonylureas	ACE inhibitors	5	1271	n/a	n/a	n/a	n/a	n/a
Iron salts	Thyroid hormones	3	350	n/a	n/a	n/a	n/a	n/a
Anticoagulants	Corticosteroids	5	1662	n/a	n/a	n/a	n/a	n/a
Anticoagulants	Acetaminophen	4	8833	n/a	n/a	n/a	n/a	n/a
Antacids	Iron salts (oral)	3	135	n/a	n/a	n/a	n/a	n/a
Anticoagulants	Proton pump inhibitors	5	5396	n/a	n/a	n/a	n/a	n/a
Proton pump inhibitors	Imidazoles	3	169	n/a	2 & 3	9 (2) 470 (3)	2 & 3	22 (2) 387 (3)
β-Adrenergic blockers	Calcium salts (oral)	n/a	n/a	n/a	n/a	n/a	n/a	n/a
ACE inhibitors	Angiotensin II receptor antagonists	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Anticoagulants	Statins	5	4431	n/a	3	7359	3	12595
Omeprazole	Benzodiazepines	5	4673	n/a	n/a	n/a	n/a	n/a
Anticoagulants	Vitamin E	5	0	n/a	n/a	n/a	n/a	n/a
Zinc salts (oral)	Quinolones (oral)	3	48	n/a	n/a	n/a	n/a	n/a

NSAIDS	β-Adrenergic blockers	3 & 4	5010	n/a	n/a	n/a	n/a	n/a
Clopidogrel	Salicylates	3	496	n/a	n/a	n/a	n/a	n/a
Oral contraceptives	Corticosteroids	5	62	n/a	n/a	n/a	n/a	n/a
β-Adrenergic blockers	Nifedipine and derivatives	5	8296	n/a	n/a	n/a	n/a	n/a
Corticosteroids/corticotropin	Anticholinesterases	n/a	n/a	n/a	n/a	n/a	n/a	n/a
ACE inhibitors	NSAIDS	4	3595	n/a	n/a	n/a	n/a	n/a

[a] Alert warnings were included in the Belgian database for 15 class-based alerts but the system was activated for none of the class-based alerts.
[b] Data from 2012 for the US Inpatient system, from 2009 till 2011 for all other systems.

4) *How many individual drug-drug combinations were included in these 33 'low-priority' class-based DDIs and how did their severity level vary both within and between different systems?*

There were 3,792 individual drug-drug combinations included in the 33 low-priority, class-based DDIs listed in the original paper.[2] Of these, 2,479 (65.4%) were included in the Belgian system, 19 (0.5%) in both the BICS and LMR systems, and none in the UK and Korean system. Most combinations that were included in the BICS and LMR system were also included in the Belgian system, except for the individual drug-drug combination '*niacin and fluvastatin'* from the class-based DDI (niacin – statins) and '*omeprazole and voriconazole'* from the class-based DDI (proton pump inhibitors – imidazoles).

5) *How many 'low-priority' DDI alert warnings were triggered to users of each of the different international EHR systems and how often were these overridden?*

The US inpatient and outpatient systems generated 38 and 237 interruptive alerts (requiring provider action) for the Level 2 class-based DDIs '*niacin and statins'* and '*proton pump inhibitors and imidazoles'*, respectively. These interruptive alerts accounted for 0.5% of the alerts in the US inpatient system and 1.0% of the alerts in the US outpatient system. Both U.S. systems generated a total of 8,276 (inpatient) and 22,665 (outpatient) Level 3 information-only alerts, which accounted for 99.5%, and 99.0% of the alerts fired in the US inpatient and US outpatient systems, respectively. The override rate for the interruptive alerts requiring provider action was higher for the US inpatient system: 57.9% and 66.7 % for the US inpatient and US outpatient system, respectively. A summary of the low-priority alert results is provided in table 6.

Table 6: An overview of the interruptive/non-interruptive nature of the low priority class-based DDIs and the total number of alerts triggered in the Belgian and US systems.

		Belgium	*US Inpatient*[b]	*US Outpatient*
Class-based alerts included		**0** (24[a])	**3**[c]	**3**[c]
Interruptive class-based alerts	Hard stops	-	0	0
	Provider action required	-	2[c]	2[c]
Non-interruptive/informational class-based alerts		-	3[c]	3[c]
Individual combinations included		**(2,479[a])**	**19**	**19**
Interruptive alerts	Hard stops	-	0	0
	Provider action required	-	11	11
Non-interruptive/informational alerts		-	8	8
Total alerts fired		**0** (53,437[a])	**8,314**	**22,902**
Interruptive alerts	Hard stops	-	0	0
	Provider action required	-	38	237
	Override rate (%)	-	57.9%	66.7%
non-interruptive alerts fired		-	8,276	22,665

[a] Alert warnings were included in the database for 24 class-based alerts (2,479 combinations) but alerts were not active for any of these (53,437 alerts could have been triggered)
[b] Data from 2012 for the US Inpatient system, from 2009 till 2011 for all other systems
[c] In the US inpatient and outpatient systems, class-based interactions could have several severity levels because individual drug pairs were assigned different severity levels.

DISCUSSION

We investigated whether alert warnings for the previously defined, 15 high-priority and 33 low-priority class-based DDIs were present in five international EHRs. We found that the high-priority alerts were mostly present, but overriding them was too easy in most of the systems, which represents an important patient safety issue. The tranylcypromine and procarbazine interaction was only included in both US systems. This particular interaction can result in a possible *fatal hypertensive crisis* in patients.[21] In Belgium, tranylcypromine and procarbazine were not available on the market, but alerts for specific drug-drug interactions containing these drugs (e.g., tranylcypromine and linezolid) were still activated in case they were imported from abroad. Tranylcypromine and tizanidine are not recommended treatments at UHBFT and as such were not available to be prescribed in PICS. Similarly, ramelteon and irinotecan were not available to be prescribed in PICS because ramelteon is not licensed in the UK, and irinotecan and other anti-cancer therapies were are largely still prescribed on paper. As a consequence, DDI alerts involving these drugs were not included in the UK system. The Korean system did not alert for the high-priority class-based DDI, strong CYP3A4 inducers and protease inhibitors, which can lead to severe hepatocellular toxicity and sub-therapeutic serum concentrations of protease inhibitors.[21, 22] The alert was triggered in both the US outpatient and UK system and the combination was also prescribed in the Belgian system.

There was huge variation in the number of individual drug-drug combinations included within the high-priority class-based interactions of different EHRs. McEvoy et al. also reported a lack of standardization in high-priority DDI levels across 14 different vendor-based EHRs in the US.[15] Our study reported a similar lack of standardization in DDI levels in EHRs in different countries and in in-house created knowledge bases. The characteristics of the databases supporting the CDS played a very important role. The Belgian system used the commercially available DelphiCare® knowledge base which is very comprehensive while the Korean system was supported by a smaller national database.

However, in the Belgian system, many alerts were not active which was a decision taken by the institution. Institutional decisions seem to be as important as database limitations in influencing which alerts were triggered. The clinical relevance of DDIs did not appear to be standardized across institutions, perhaps due, in part, to the supporting evidence often being theoretical or limited to case reports. A framework for the standardized evaluation of the clinical relevance of DDIs may be required. The absence of hard stops in the Belgian system could be explained by the reluctance in this specific institution to include hard stops.

We also evaluated the implementation and alerting of the low-priority DDI list. The low-priority alerts were not present in most EHRs. The US inpatient and outpatient systems were the only systems that had alerts for three of the 33 low-priority class-based DDIs. Although there was only a small number of interruptive alerts generated, these alerts could still be safely made non-interruptive to reduce the alert burden.[14] The absence of any alerts for the other DDIs may involve a safety risk. Completely turning off the low-priority alerts is not recommended. Prescribers should have access to non-interruptive alerts or on-demand information regarding these low-priority DDIs.

Finding the right balance between over- and under-alerting is essential to avoid alert fatigue. Similar to McEvoy et al., we believe that institutions should carefully review their DDI alerting approaches.[15] This process should be iterative; implementation of CDS should not be considered a ‘one and done’ step but a continuous process improvement. A review may be required following updates in the evidence supporting specific DDIs, but also based on an evaluation of alert overrides and override reasons. Sharing DDI information between institutions could also help in understanding the broader perspective of alerting approaches and make the knowledge management process less burdensome and more informed.

Future research should evaluate strategies to improve the clinical relevance of alerts including context-aware alerting (based on individual patient data), using DDI specific screening intervals (time

between the administrations of two drugs for which an alert is triggered) and applying human factor principles. [4, 23-26]

We have acknowledged that not all institutions in our study could provide alert data for the initially defined time period and so we have only provided relative descriptive comparisons. We used a convenience sample of five EHRs and generalizability of the results may be limited to academic medical centers with in-house created knowledge bases. The comparison was limited to the previously published high-priority and low-priority DDI list which is not an official standard. Additionally, it is possible that the research that contributed to the high priority paper helped influence the DDI alert implementations in the Boston inpatient and outpatient setting. This could have led to the US hospitals having a greater concordance with the cited alerts than the other international institutions. However, we also evaluated changes in DDI severity classification during the study period and only a few DDIs changes were observed.

CONCLUSION

Alert warnings were found to be present in the different EHRs for the majority of the high-priority DDIs but only for a few low-priority DDIs. However, some very important warnings were overridden in some systems. All systems should include some hard stops, though they should be using sparingly. The specific combinations that were included and the severity level assigned often varied substantially. A framework for the standardized evaluation of the clinical relevance of DDIs is required. Institutions should also review their DDI alerting strategy, especially after the publication of updated evidence, and share DDI alerting information between institutions to promote learning. Future research should focus on achieving the right balance between over- and under-alerting.

Acknowledgements

Pieter Cornu received a research grant from the Wetenschappelijk Fonds Willy Gepts of the UZ Brussel.

Insook Cho was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (NRF-2016R1D1A1A09919502).

This study was funded by grant #U19HS021094 from the Agency for Healthcare Research and Quality (AHRQ).

Conflict of interests

The authors have no conflicts of interest regarding this study.

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