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Differences of Reasons for Alert Overrides on Contraindicated Co-prescriptions by Admitting Department

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Objectives: To reveal differences in drug-drug interaction (DDI) alerts and the reasons for alert overrides between admitting departments. **Methods:** A retrospective observational study was performed using longitudinal Electronic Health Record (EHR) data and information from an alert and logging system. Adult patients hospitalized in the emergency department (ED) and general ward (GW) during a 46-month period were included. For qualitative analyses, we manually reviewed all reasons for alert overrides, which were recorded as free text in the EHRs. **Results:** Among 14,780,519 prescriptions, 51,864 had alerts for DDIs (0.35%; 1.32% in the ED and 0.23% in the GW). The alert override rate was higher in the ED (94.0%) than in the GW (57.0%) ($p < 0.001$). In an analysis of the study population, including ED and GW patients, 'clinically irrelevant alert' (52.0%) was the most common reason for override, followed by 'benefit assessed to be greater than the risk' (31.1%) and 'others' (17.3%). The frequency of alert overrides was highest for anti-inflammatory and anti-rheumatic drugs (89%). In a subanalysis of the population, 'clinically irrelevant alert' was the most common reason for alert overrides in the ED (69.3%), and 'benefit assessed to be greater than the risk' was the most common reason in the GW (61.4%). **Conclusions:** We confirmed that the DDI alerts and the reasons for alert overrides differed by admitting department. Different strategies may be efficient for each admitting department.

Keywords: Contraindications, Drug Interactions, Clinical Decision Support Systems, Hospital Admitting Department

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I. Introduction

Drug-drug interactions (DDIs) are defined as 'the pharmacological or clinical response to the administration of a drug combination, different from that anticipated from the known effects of the two agents when given alone' [1]. DDIs are one of the main causes of adverse drug events [2,3]. DDI events are more frequent during hospitalization than in ambulatory settings because of intensive medication, treatment by multiple physicians, and transfer between departments [2,4,5]. Many hospitals have adopted clinical decision support systems (CDSSs) with a DDI alerting function to improve the quality and efficiency of care and to increase patient safety

by reducing medication errors [6,7]. However, high rates of alert overrides have been reported for DDI alerts [8,9] because of clinically inappropriate alerts [10-12], 'alert fatigue' due to excessive alerts [13], or intended prescriptions [10].

Many studies have defined the characteristics and risks of DDI alerts and their overrides to make DDI alerting systems more acceptable to prescribers [14-19]. Patient age, comorbidity, hospitalization, number of medications prescribed per day, and number of prescribers are known risk factors for DDIs [5,20,21]. Becker et al. [22] reported that non-steroidal anti-inflammatory drugs, diuretics, cardiac glycosides, and calcium channel blockers have higher risks of DDIs than other drugs. However, these known risk factors for DDI alerts were derived from a single clinical setting and different study designs [5,20-22]. Thus, their results cannot be generalized to different clinical settings.

To reveal whether a specific clinical setting is a risk factor for DDI alerts and alert overrides, we previously performed a study encompassing three different clinical settings, and found that admission to the emergency department (ED) is an independent risk factor for DDI alerts and alert overrides, with higher risks, as compared to the general ward (GW) and intensive care unit [23]. However, we were unable to determine why admission to the ED is more critical for risk of DDI alerts and alert overrides than admission to other departments because the study was designed as a quantitative analysis.

If the drug pairs causing DDI alerts and reasons for alert overrides are different between admitting departments, then strategies to reduce DDI alerts and alert overrides must also be different for each department. Thus, in this study, we explored differences in drug pairs causing DDI alerts and reasons for alert overrides between the ED and GW by analyzing longitudinal Electronic Health Record (EHR) data and alert and logging system information from a teaching hospital.

II. Methods

A retrospective observational study was performed using longitudinal EHR data and information from an alert and logging system. The study was reviewed and exempted by the Institutional Review Board of Ajou University Hospital.

1. Clinical Setting and Study Population

The study hospital is a tertiary teaching hospital with 1,099 patient beds and 22 operating rooms. All prescriptions at the hospital were prescribed by computerized provider order entry (CPOE) and recorded in EHRs. All patients hospitalized between September 1, 2009 and June 30, 2013, were included in the study population. The enrollment criteria for this study included admission to either of two departments (ED or GW) during the study period, and prescription of any enteral or parenteral medication. Because of the fluctuations in individual drug effects according to dose or underlying conditions in pediatric patients, we enrolled patients aged over

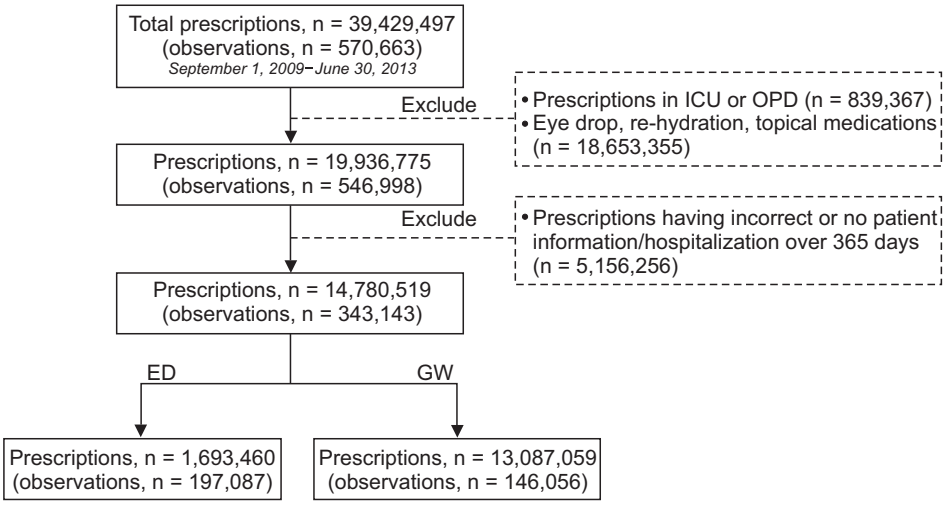

Figure 1. Flowchart showing prescriptions and observations included in the study. All prescriptions in the emergency department (ED) and general ward (GW) from September 1, 2009 to July 31, 2013, were included (n = 39,429,497; number of observations = 570,663). Multiple visits or admissions of a patient were counted separately. Thus, the observations may include the same patient more than once. We excluded eye drops, re-hydration solutions, and topical medications, patients who only visited the out-patient department (OPD) or were admitted to the intensive care unit (ICU), patients with no demographic information, and patients hospitalized for over 365 days. There were 1,693,460 prescriptions in the ED (197,087 observations) and 13,087,059 prescriptions in the GW (146,056 observations).

18 years (Figure 1). Outpatient data were not included in the analyses, because main prescribers and reimbursement policy are quite different to those in the inpatient setting. We excluded topical medications, eye drops, and re-hydration solutions from analyses because the DDI rule set has no information on their formulas. Patients with no demographic information were excluded. We also excluded patients hospitalized for over 365 days because of different underlying disease due to long-term hospitalization.

2. Study Design and Definitions

When a patient visited the ED or was admitted to the GW multiple times, each visit or admission was considered an independent observation. The mean number of drugs per day was defined as all prescriptions prescribed divided by number of hospital days during the observation period. Prescriptions entered by nurses as well as physicians were included in the analyses. Each alert that occurred during observation was counted independently. All prescriptions associated with alerts were tagged with three-digit Anatomical Therapeutic Chemical Classification System (ATC) codes for grouping. When an alert is to be overridden in the system, the physician has to choose one of the following two options: 1) provide the reason for the alert override or 2) cancel and/or change the prescription. The reasons for alert overrides were recorded as free text in the EHR system. We classified the reasons into three categories by manual review: 'clinically irrelevant alert', 'benefit assessed to be greater than the risk', and 'others' (Table 1). This classification was modified from the study of Grizzle et al. [24] and simplified according to the data from this study.

Table 1. Categories of reasons for alert overrides

Clinically irrelevant alert
Drug-drug interaction (DDI) alerts between prescriptions for in-hospital medication and discharge medication
DDI alerts caused by prescriptions having different medication time
Different route or formula of a same ingredient
Benefit assessed to be greater than the risk
For treatment of a specific symptom
Physician's judgment on the clinical situation
Prescriptions under close observation
Others[a]

The reasons for alert overrides recorded as free text in Electronic Health Records were categorized into three categories by the authors: 'clinically irrelevant alert', 'benefit assessed to be greater than the risk', and 'others'. Also, each category has sub-groups for detailed clinical situations.

[a]Clinically meaningless characteristics.

Table 2. Basic characteristics of subjects and DDI alerts by admitting department

	Total participants	Admitting department		*p*-value
		ED	GW	
Observations (visit or admission)	343,143 (100)	197,087 (57.4)	146,056 (42.6)	
Age (yr)	51.2 ± 17.8	49.2 ± 18.3	53.9 ± 16.7	<0.001
Female[a]	168,710 (49.2)	95,783 (48.6)	72,927 (49.9)	<0.001
Hospital stay (day)	4.2 ± 10.4	1.0 ± 0.1	8.5 ± 14.9	<0.001
Number of drugs per day	9.6 ± 8.4	8.6 ± 9.5	11.1 ± 6.4	<0.001
Prescriptions	14,780,519 (100)	1,693,460 (11.5)	13,087,059 (88.5)	
Discharge prescriptions[a]	1,092,001 (7.4)	366,171 (21.6)	725,830 (5.5)	<0.001
DDI alerts	51,864 (100)	22,322 (43.0)	29,542 (57.0)	
Alerts by transfer (ED to GW)[a]			304 (1.0)	
Alert overrides[a]	35,231 (67.9)	20,993 (94.0)	14,238 (48.2)	<0.001

Values are presented as number (%) or mean ± standard deviation.

p-value indicate the results of χ^2 tests for categorical variables or *t*-tests for continuous variables. Age was recorded at admission. Hospitalization was number of days from admission to discharge. Number of drugs per day was the mean number of prescribed drugs per day per observation. Discharge prescriptions were counted using check-up tags from prescribers in the Electronic Health Records. Alerts by transfer were alerts for possible DDIs between ED and GW prescriptions when a patient was transferred from the ED to the GW.

DDI: drug-drug interaction, ED: emergency department, GW: general ward.

[a]Number of proportions considered within each department (all, ED, and GW).

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3. CDSS and DDI Rules of the Study Hospital

Official governmental rules revised by the Ministry of Food and Drug Safety were used in the study hospital [25]. The rules on DDI alerts provide information on possible drug interactions, effects of interactions, the mechanism and severity of drug interactions, and references. Duplication of prescriptions within the same therapeutic class, so-called therapeutic duplication, was also included. If a prescriber prescribed medicines through a CPOE or EHR system, all combinations of current and past prescriptions within 24 hours were compared using the official governmental DDI rules. If there is a DDI between drugs, then the DDI alert system generates an alert for the DDI and provides associated information. Only in-hospital prescriptions were considered by the alerting system.

Table 3. Top five most frequent alerts and overrides by admitting department

Class of drug 1	Class of drug 2	Alerts	Alert overrides
Alert in ED and GW			
Anti-inflammatory and anti-rheumatic products	Anti-inflammatory and anti-rheumatic products	31,094 (60.0)	25,331 (71.9)
Anti-inflammatory and anti-rheumatic products	Analgesics	3,208 (6.2)	2,343 (6.7)
Mineral supplements	Diuretics	2,953 (5.7)	1,342 (3.8)
Cardiac therapy	Drugs for obstructive airway diseases	2,534 (4.9)	871 (2.5)
Diuretics	Antibacterials for systemic use	2,152 (4.2)	993 (2.8)
Other drug pair		9,923 (19.1)	4,351 (12.4)
Total (ED + GW)		51,864 (100)	35,231 (67.9)
Alerts in ED			
Anti-inflammatory and anti-rheumatic products	Anti-inflammatory and anti-rheumatic products	19,497 (87.3)	18,687 (89.0)
Anti-inflammatory and anti-rheumatic products	Analgesics	717 (3.2)	626 (3.0)
Drugs for obstructive airway diseases	Drugs for obstructive airway diseases	689 (3.1)	614 (2.9)
Mineral supplements	Anti-inflammatory and anti-rheumatic products	400 (1.8)	340 (1.6)
Diuretics	Mineral supplements	277 (1.2)	220 (1.0)
Other drug pair		742 (3.3)	506 (2.4)
Total (ED)		22,322 (100)	20,993 (94.1)
Alerts in GW			
Anti-inflammatory and anti-rheumatic products	Anti-inflammatory and anti-rheumatic products	11,597 (39.3)	6,644 (46.7)
Mineral supplements	Diuretics	2,676 (9.1)	1,122 (7.9)
Anti-inflammatory and anti-rheumatic products	Analgesics	2,491 (8.4)	1,717 (12.1)
Cardiac therapy	Drugs for obstructive airway diseases	2,292 (7.8)	698 (4.9)
Diuretics	Antibacterials for systemic use	2,002 (6.8)	876 (6.2)
Other drug pair		8,484 (28.7)	3,181 (22.3)
Total (ED)		29,542 (100)	14,238 (48.2)

Values are presented as number (%).

Drug pairs triggering alerts frequently in each admitting department, and numbers of alerts and alert overrides are shown. Drugs were classified using three-digit Anatomical Therapeutic Chemical Classification System (ATC) codes. Alerts were counted by the system log when prescriptions were made. Alert overrides were counted by examination of text records of reasons for alert overrides.

ED: emergency department, GW: general ward.

4. Statistical Analyses

Total numbers of patients, prescriptions, and alerts were estimated by the admitting department. We report continuous variables as the mean and standard deviation and categorical variables as numbers and percentages. The prevalence of DDI alerts was compared between groups using t-tests and chi-square tests. For all tests, a two-tailed p-value of <0.05 was considered to indicate statistical significance. All analyses were performed using PASW ver. 18 for Windows (SPSS Inc., Chicago, IL, USA).

III. Results

We identified 343,143 visits or admissions to the ED or GW during the study period. An illustration of how patients were included in the study is shown in Figure 1. Table 2 shows the basic characteristics of the study participants by admitting department. Patients who visited the ED (49.2 ± 18.3 years) were younger than patients admitted to the GW (53.9 ± 16.7 years) ($p < 0.001$). The number of drugs per day was higher in the GW (11.1 ± 6.4) than in the ED (8.6 ± 9.5) ($p < 0.001$). In the ED, 21.6% of all prescriptions were for discharge medications, as compared to 5.5% in the GW ($p < 0.001$). The prevalence of DDI alerts in the ED (1.3%) was significantly higher than that in the GW (0.2%) ($p < 0.001$). A total of 304 alerts in the GW (1.0%) were related to prescriptions due to transfer between the ED and GW. The rate of alert overrides was higher in the ED (94.0%) than the GW (57.0%) ($p < 0.001$).

The top five most frequent DDI alerts and their overrides by admitting department are shown in Table 3. Therapeutic duplication between anti-inflammatory and anti-rheumatic products was the most frequent cause of alerts and alert overrides in this study; 60.0% of alerts were for therapeutic duplication between anti-inflammatory and anti-rheumatic products (87.3% of alerts in the ED and 39.3% of alerts in the GW). Such therapeutic duplication was the cause of 71.9% alert overrides (89.0% in the ED and 46.7% in the GW). The next most common alerts were for DDIs between anti-inflammatory and anti-rheumatic products and analgesics, mineral supplements and diuretics, and cardiac drugs and drugs for obstructive airway diseases, in that order.

Table 4 shows the reasons for alert overrides by admitting department. 'Clinically irrelevant alert' (51.6%) was the most common reason, followed by 'benefit assessed to be greater than the risk' (31.1%) and 'others' (17.3%), in that order. Of the clinically irrelevant alerts, alerts relating to DDIs between in-hospital and discharge medications were dominant, accounting for 43.0% of all alert overrides. They were especially high in the ED (accounting for 66.6% of all alert overrides in the ED).

Table 4. Reasons for alert overrides by admitting department

Category of alert overrides reasons	Total alerts		
	Total	ED	GW
Clinically irrelevant alert	18,170 (51.6)	14,547 (69.3)	3,623 (25.4)
DDI alerts between prescriptions for in-hospital medication and discharge medication	15,162 (43.0)	13,982 (66.6)	1,180 (8.3)
DDI alerts caused by prescriptions having different medication time	2,759 (7.8)	433 (2.1)	2,326 (16.3)
Different route or formula of a same ingredient	249 (0.7)	132 (0.6)	117 (0.8)
Benefit assessed to be greater than the risk	10,960 (31.1)	2,213 (10.5)	8,747 (61.4)
For treatment of a specific symptom	8,739 (24.8)	1,804 (8.6)	6,935 (48.7)
Physician's judgment on the clinical situation	1,791 (5.1)	315 (1.5)	1,476 (10.4)
Prescriptions under closed observation	430 (1.2)	94 (0.4)	336 (2.4)
Others[a]	6,101 (17.3)	4,233 (20.2)	1,868 (13.1)
Total	35,231 (100)	20,993 (59.6)	14,238 (40.4)

Values are presented as number (%).

Reasons for alert overrides were counted using data from Electronic Health Records. Three categories of reasons for alert overrides were used by the authors. Reasons for alert overrides for prescriptions of anti-inflammatory and anti-rheumatic drugs, which were the most common overrides in total and in each admitting department, were also counted.

DDI: drug-drug interaction, ED: emergency department, GW: general ward.

[a]Clinically meaningless characteristics.

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IV. Discussion

We analyzed 46 months of EHR data from a tertiary teaching hospital, including 14,780,519 prescriptions and 51,864 DDI alerts from 343,143 observations, to determine whether the drug pairs causing DDI alerts and the reasons for alert overrides differ by department. For the qualitative analyses, we manually reviewed all the reasons for alert overrides.

We minimized recall bias by analyzing all prescription data in the system log file. All admissions and prescriptions were identified using a clinical database containing detailed time-stamped records. All DDI alerts and alert overrides that occurred in the hospital during the study period were included. We used prevalence of alerts and alert overrides instead of incidence to explore 'alert fatigue' that prescribers feel, and to obtain the characteristics of repeated alert overrides. The prevalence can be directly compared with the values from previous studies because we used the same index as they did. All of the reasons for alert overrides, recorded as free text, were manually categorized by the authors for accurate analyses.

The total prevalence of DDI alerts was 0.4%, lower than the values reported by studies by Isaac et al. [26] (6.4%), Taylor and Tamblyn [27] (6.6%), and Zwart-van Rijkom et al. [28] (27.8%). The lower prevalence in this study could be explained by differences in the scope of DDI rules between the study hospital and the other hospitals, and by the reimbursement policy of the Korean government for drugs violating the DDI rules. The DDI rules in other studies included DDIs that may have potential clinical relevance or quality of evidence [28]. However, in our study, only obligatory DDIs that may cause refusal of reimbursement were included. In Korea, all prescriptions are reviewed by the Health Insurance Review & Assessment Service (HIRA) according to the National Health Insurance Act.

The most frequent cause of DDI alerts and alert overrides was therapeutically duplicated prescriptions of anti-inflammatory and anti-rheumatic drugs. Considering the frequent occurrence of alerts and alert overrides, it seems that most duplicated prescriptions of anti-inflammatory and anti-rheumatic drug pairs may have clinically legitimate reasons. As pain is one of main reasons for visiting a hospital, prescription of pain relievers is very common in hospitals [29]. Therefore, the chance of DDI alerts for pain relievers may be higher than that for other prescriptions. Other high-risk drug pairs for DDI alerts are analgesics, diuretics, cardiac drugs, drugs for obstructive airway diseases, and antibacterials for systemic use. These results are similar to those of previous reports; however, the order of drug pairs for DDI alerts differs among studies [2,8]. These differences may be caused by different rules for DDI alerts, different prescription patterns, and/or different clinical environments.

We found that DDI alerts and reasons for alert overrides differed between two admitting departments. The most common reason for alert overrides in the ED was 'clinically irrelevant alert', whereas 'benefit assessed to be greater than the risk' was the most common reason in the GW. Alert overrides due to discharge medications accounted for most clinically irrelevant alerts in the ED (96.1%). As discharge medications are not intended to be used together with in-hospital medications, the alerts might be inappropriate. Clinically irrelevant alerts are known to be the main cause of alert fatigue [13], and most of them are ignored [30,31]. The DDI rules of the study hospital do not consider route of medication or drug dose, but only consider the drug ingredient. These simple rules might explain the high prevalence of alert overrides. Adding a rule that excluding alerts for DDIs between discharge medications and in-hospital medications may reduce the irrelevant alerts in the system. Considering these results, improving the alerting rules for discharge prescriptions may prevent two-thirds of the inappropriate alerts in the ED at the study hospital.

The second most common reason for alert overrides was 'benefit assessed to be greater than the risk' (31.1%). 'For treatment of a specific symptom' was the most common reason for 'benefit assessed to be greater than the risk'. We suppose that prescribers override alerts with the intention of treating symptoms, such as abnormal laboratory test results or unstable vital signs, in spite of possible DDIs. We may need a more sophisticated approach in this case, which differs from that for clinically irrelevant alerts. For example, DDI rule updates in conjunction with dynamic patient information (e.g., lab results, drug elimination capacity, and vital signs), as mentioned in previous studies, may be effective [7,32,33]. However such sophisticated approaches are usually hard to develop and adopt.

In this study, 17.3% of all alert overrides had clinically meaningless reasons. This is lower than the value reported by Grizzle et al. [24] (84.3%). For the reason 'others', it was difficult to assess the physicians' prescribing. The 'others' category consisted only of consonants, vowels, and meaningless terms. When a physician prescribes, sometimes they enter arbitrary reasons. The system cannot judge their reasonability. The CDSS could not provide the appropriateness of prescriptions systematically. The appropriateness of prescription is a problem for the HIRA. The HIRA reviews the reason and makes a decision as to whether the contraindicated co-prescription was acceptable or not. If the reason was unac-

ceptable, the insurance payment is curtailed.

Our analyses have important limitations. As with other retrospective analyses, we could not consider unknown confounding factors that may affect the study outcomes. Our study may have selection bias because data from only one institution were used. The study population was derived from a teaching hospital, which may be a quite different clinical setting to that of general hospitals or private clinics. The prescriptions for out-patients are under strict control by HIRA. And there may be differences in prescription patterns between in-patient and out-patient settings. As we excluded the out-patient setting in this study, our results may not reflect the general clinical setting, including out-patient departments. We analyzed drug pairs using three-digit ATC codes. This might have caused loss of detailed information at the individual drug level. However, the purpose of this study was to understand differences in the characteristics of and reasons for alert overrides between the ED and GW, rather than to understand individual drug pairs that cause DDIs.

In conclusion, we confirmed that DDI alerts and the reasons for alert overrides differed by admitting department. We may need different strategies for each department to reduce DDI alerts and alert overrides. Improving alerting rules for discharge prescriptions may prevent two-thirds of all inappropriate alerts in the ED. Sophisticated DDI rule updates, considering the patient's clinical information, may be required for the GW to make the alerting system acceptable to prescribers.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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