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Overriding Drug-Drug Interaction Alerts in Clinical Decision Support Systems: A Scoping Review

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Abstract

Ineffective computerized alerts for potential Drug-Drug Interactions (DDI) is a longstanding informatics issue. Prescribing clinicians often ignore or override such alerts due to lack of context and clinical relevance, among various other reasons. In this study, we reveiwed published data on the rate of DDI alert overrides and medications involved in the overrides. We identified 34 eligible studies from sites across Asia, Europe, the United States, and the United Kingdom. The override rate of DDI alerts ranged from 55% to 98%, with more than half of the studies reporting the most common drug pairs or medications involved in acceptance or overriding of alerts. The high prevalance of alert overrides highlights the need for decision support systems that take user, drug, and institutional factors into consideration, as well as actionable metrics to better characterize harm associated with overrides.

Keywords:

Drug interactions; Medical Order Entry Systems; Review

Introduction

Drug-drug interactions (DDIs) are responsible for 5-14% of adverse drug reactions in hospitalized patients [1] and a major risk factor for hospitalization, particularly among elderly ambulatory patients [2]. While there are multiple opportunities to prevent adverse drug events at the medication ordering, dispensing, and administration phases of the drug use process, it is extremely challenging for prescribers to identify potentially dangerous DDIs, given the high number of prescriptions as well as possible combinations of drug interactions [3]. To overcome this challenge, computerized physician orders in combination with clinical decision support systems (CDSS) offer an opportunity to detect potential DDIs and alert prescribers [4]. However, alert fatigue has been recognized as a major limitation during routine clinical use and workflow [5]. Acceptance and effectiveness of DDI alerts depend on their real clinical implications. Alerts with low specificity will not only produce alert fatigue, but also lead to overriding i.e., ignoring or not acting upon an alert [6].

The major reasons for overriding DDI alerts are thought to be alert fatigue and poor usability; however, recent research suggests a multifaceted scenario, including inaccurate warnings, little value for prescribers in terms of clinical relevance, or incorrect judgments by the prescriber [7]. There are numerous studies that have examined this issue of overriding medication warnings, and these studies have identified various features that may increase override rates. Therefore, the objective of this study is to determine the prevalence of overriding DDI alerts from CDSS by performing a scoping review of the literature. Specifically, we sought to (1) determine the frequency with which prescribers override DDI alerts and (2) determine those drug pairs most often involved in the overrides.

Methods

The concept of importance for this scoping review is frequency of prescription overrides when a potential drug-drug interaction alert is triggered in an inpatient or outpatient facility.

Search Strategy

This scoping review included studies published after January 1, 2000 and provided override data related to drug-drug interaction alerts. The search was limited to Embase, PubMed, Scopus, and Web of Science databases using the following keywords: “drug-drug interactions”, “interaction”, “drug-interaction”, “override”, “order override”, “prescription override,” and variations. In addition, references of all identified articles were searched for additional reports.

Data extraction

Two researchers (LZV and VS) participated in the data extraction process. Relevant data were extracted from the included studies to address drug-drug interaction override occurrence, considering the following inclusion criteria: (1) reports published in English with desired outcomes reported, and (2) override alerts and override rates due to DDI were reported. Data extracted included the following: title, year of publication, city or country of origin, setting (inpatient or outpatient), number of drug-drug interaction alerts, percentage of those alerts overridden, reason for overriding, and top drug classes or pairs involved in overridden alerts.

Results

Our literature search identified 236 studies potentially eligible for inclusion. Of these studies, 106 were excluded due to duplication and 39 were excluded because they were not relevant to the topic of study. The full text of the remaining 93 were screened, of which 59 did not meet the inclusion criteria, leaving 34 studies to be included in the study.

Of the 34 studies, 22 (65%) were conducted in the United States, 7 (20%) in Asia and 5 (15%) in Europe and the United Kingdom. Nineteen studies (56%) were conducted in inpatient facilities, 10 (29%) in outpatient facilities and 5 (15%) in both types of facilities. The time frame in which alert override occurrence was evaluated in these studies ranged from 4 days to 46 months. The number of DDI alerts varied depending on the size and type of the healthcare facility and the time frame of the study (see Table 1).

The override rate of DDI alerts ranged from 55% to 98% in U.S sites and 57% to 95% in non-US sites. Twenty studies (59%) identified pairs or single medications involved in the DDI alert.

The medications that most commonly contributed to alerts in these studies included angiotensin-converting enzyme (ACE) inhibitors (e.g., enalapril, captopril, etc.), anticoagulants (e.g., warfarin, apixaban, rivaroxaban, etc), beta-adrenergic blocking agents (e.g., propranolol, atenolol, metoprolol, etc.), diuretics (e.g., hydrochlorothiazide, furosemide, etc.), nonsteroidal anti-inflammatory drugs (e.g., ibuprofen, naproxen, diclofenac, etc.) and QTc-prolonging agents (e.g., amiodarone, ondansetron, azithromycin, etc).

Provider Rationale for Overrides

Eighteen studies (53%) provided reasons for overriding the alerts. The most common reasons were "benefit outweighs the risk", "clinician would monitor", "alert fatigue" and "patient had already tolerated combination".

Table 1 – Characteristics of studies reporting drug-drug interaction and prescription override rates

Author, Year organized chronologically	**Clinical Setting**	**Study Length** (months)	**# DDI Alerts**	**DDI Alerts Overridden (%)**	**State, Country**	**# sites**
Payne, 2002 [8]	All	1	108	95 (88)	WA, USA	2
*Weingart, 2003 [9]	Outpatient	3	3,129	2959 (95)	MA, USA	1
Shah, 2006 [10]	Outpatient	5	1,078	627 (58)	MA, USA	31
*Indermitte, 2007 [11]	Outpatient	1	510	289 (57)	Switzerland	15
*Mille, 2008 [12]	Inpatient	2	3,404	2,337 (69)	France	1
*van der Sijs, 2008 [13]	Inpatient	1	3,089	1963 (64)	Rotterdam, The Netherlands	1
Lin, 2008	Inpatient	0.2	85	74 (87)	WA, USA	1
*Weingart, 2009 [14]	Outpatient	6	133,051	121,168 (91)	MA, USA	NR
*van der Sijs, 2009 [15]	Inpatient	24	NR	8,846 (NR)	Netherlands	1
*Isaac, 2009 [16]	Outpatient	8	229,663	208,534 (91)	MA, NJ, PA, USA	NR
Seidling, 2010 [17]	Inpatient	12	15,632	14,075 (90)	MA, USA	1
Jani, 2011 [18]	Inpatient	12	3,507	3,119 (89)	UK	1
*Slight, 2013 [19]	Outpatient	36	24,849	14,966 (60)	MA, USA	2
Duke, 2013 [20]	Outpatient	6	2140	1,789 (84)	IN, USA	1
*Yeh, 2013 [21]	Outpatient	24	11084	10142(92)	Taipei, Taiwan	1
Ahn, 2014 [22]	Inpatient	18	6060	4,409 (73)	Korea	1
*Ahn, 2014 [23]	Inpatient	46	51864	35,231 (68)	Korea	1
Bryant, 2014 [24]	Inpatient	0.1	1157	1097 (95)	WA, USA	2
Knight, 2015 [25]	Inpatient	7	18,894	18,640 (98)	MD, USA	1
*Nasuhara, 2015 [26]	All	12	170	111 (65)	Japan	1
Beeler, 2015 [27]	Outpatient	36	24,849	13,766 (55)	MA, USA	2
Cho I, 2016 [28]	All	4	21,859	17,487 (80)	Korea	3
*Wong, 2017 [29]	Inpatient	3	NR	6,565 (NR)	MA, USA	1
*Wong, 2017 [30]	Inpatient	36	NR	7,642 (NR)	MA, USA	1
Straichman, 2017 [31]	Inpatient	12	145,103	137,415 (95)	Tel Aviv, Israel	1
*Humphrey, 2018 [32]	Inpatient	24	41,471	36,988 (89)	MA, USA	1
Rehr, 2018 [33]	Inpatient	6	NR	15 (NR)	MA, USA	1

*Wright, 2018 [34]	Outpatient	12	NR	NR	MA, USA	1
Nanji, 2018 [35]	Inpatient	36	37,579	25,616 (68)	MA, USA	1
*Wong, 2018 [36]	Inpatient	10	24,231	22,292 (92)	MA, USA	1
*Cho I, 2019 [37]	Inpatient	4	18,360	13,155 (72)	Seoul, South Korea	1
Wright, 2019 [7]	All	12	3,096,348	2,825,785 (91)	USA	10
*Daniels, 2019 [38]	Inpatient	36	106,528	100,136 (94)	USA	1
*Edrees, 2020 [39]	All	12	16,011	15, 318 (96)	MA, USA	1

Studies that reported drug pairs or medications involved in the DDI alert overrides; NR – not reported

Discussion

The wide variation in override rates may be attributed to several factors. First, the definition of alert override and how the alerts are presented to the user may not be consistent across studies. Second, the data collection period was limited in the majority of studies, and half of studies collected override data for less than a year. Third, different institutions may value certain DDIs as more important or relevant to the populations they serve, thus prioritizing a specific group of DDI alerts over others. Last, in most settings in the US, alert notifications are generated by a just a few drug knowledge database vendors, but the studies did not report the source of DDI knowledge used in the alerting. Previous studies have also demonstrated wide discordance between what is a major DDI [40], [41].

Is override rate the right metric for quality and safety?

The variations in override rates across institutions highlight the challenges with using override rate as a metric for CDSS quality and performance analysis. In order to capture the user's intention to accept or override an alert, additional data are needed. A more actionable metric, besides the proportion of the DDI alerts overridden, could be the number of alerts that are associated with adverse event reports; however, it may be challenging to obtain underlying data for such a metric because it would require examination of medical records, in addition to the consequences of attributing harm back to exposure to a DDI. A study exploring the occurrence of adverse drug events and override appropriateness identified that adverse drug events were significantly higher with inappropriate versus appropriate overrides (9.4% versus 4.3%, respectively) [42].

Most studies report the frequency of alerts and global override, with limited to no information on the occurrence of real harm on patients. Collecting and reporting data on harm due to DDI overrides is important particularly because nearly 30% of included studies were conducted in outpatient facilities where there is limited follow-up on DDIs. Studies that reported drug pairs responsible for triggering alerts did not provide the number of patients that actually suffered an adverse event or complication due to the DDI, and those studies that reported reasons for override included options such as "will monitor" or "patient tolerated combination in the past," raising concerns about quality of care and patient safety. Thus, our findings highlight the need for additional research on assessing the potential harm associated with alert overrides.

Recommendations for future studies include investigating the impact of tailoring alerts to site-specific workflows and emphasizing the prioritization of alerts that involve documented life-threatening consequences. Alerts considered to be of low clinical relevance may be eliminated, but requires close follow-up because of variations in alert implementations or definitions of what is considered a severe DDI. For example, to improve the specificity of DDI alerts, a study conducted by Daniels et al., implemented refinements to the CDSS by identifying alerts of low importance and clinical relevance through alert analysis and interaction with clinicians and a multidisciplinary panel. These refinements decreased DDI alert frequency; however, their impact on prescription overrides and influence on patient safety was not fully assessed [38]. More studies are necessary to assess the context for triggering alerts and their clinical impacts. Alerts out of context are often irrelevant and therefore, to truly mitigate alert fatigue and associated DDI overrides, CDSS tools need to be contextualized by taking clinical, user, and institutional factors into consideration [43].

Conclusions

A significant percentage (more than 50%) of drug-drug interaction alerts generated by clinical decision support systems are overridden or ignored by prescribers. More granular data and metadata, beyond alert override or acceptance rates are needed, to understand and monitor the impact of DDI overrides on patient outcomes. Potential data elements of interest include source of DDI knowledge, prescriber's intention and action in response to an alert, and metadata related to the patient and prescriber involved in an alert. Further research is also needed to study the impact of tailoring alerts to specific settings using institutional, drug, and patient factors.

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