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SHORT COMMUNICATION

Use of an On-demand Drug–Drug Interaction Checker by Prescribers and Consultants: A Retrospective Analysis in a Swiss Teaching Hospital

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Abstract
Background Offering a drug–drug interaction (DDI) checker on-demand instead of computer-triggered alerts is a strategy to avoid alert fatigue.
Objective The purpose was to determine the use of such an on-demand tool, implemented in the clinical information system for inpatients.
Methods The study was conducted at the University Hospital Zurich, an 850-bed teaching hospital. The hospital-wide use of the on-demand DDI checker was measured for prescribers and consulting pharmacologists. The number of DDIs identified on-demand was compared to the number that would have resulted by computer-triggering and this was compared to patient-specific recommendations by a consulting pharmacist.
Results The on-demand use was analyzed during treatment of 64,259 inpatients with 1,316,884 prescriptions. The DDI checker was popular with nine consulting pharmacologists (648 checks/consultant). A total of 644 prescribing physicians used it infrequently (eight checks/prescriber). Among prescribers, internists used the tool most frequently and obtained higher numbers of DDIs per check (1.7) compared to surgeons (0.4). A total of 16,553 DDIs were identified on-demand, i.e., <10 % of the number the computer would have triggered (169,192). A pharmacist visiting 922 patients on a medical ward recommended 128 adjustments to prevent DDIs (0.14 recommendations/patient), and 76 % of them were applied by prescribers. In contrast, computer-triggering the DDI checker would have resulted in 45 times more alerts on this ward (6.3 alerts/patient).
Conclusions The on-demand DDI checker was popular with the consultants only. However, prescribers accepted 76 % of patient-specific recommendations by a pharmacist. The prescribers' limited on-demand use indicates the necessity for developing improved safety concepts, tailored to suit these consumers. Thus, different approaches have to satisfy different target groups.

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1 Background

Drug–drug interactions (DDIs) are an important cause of adverse drug events leading to increased morbidity and mortality [1–3]. As prescribing errors and resulting DDIs are potentially preventable, computerized physician order entry (CPOE) in combination with clinical decision support (CDS) offers an opportunity to minimize prescription errors [4].

However, excessive alerts of limited clinical significance induce alert fatigue [5, 6]. Hence, computer-triggered safety alerts are often ignored by prescribers [7]. Users are more likely to accept warning messages if the alerting system features enhanced usability [8]. In particular, systems with improved acceptance are characterized by both providing high quality of knowledge and presenting the messages in a user-friendly manner, including detailed advice [9].

To prevent overriding, one recent study investigated electronic hard stop alerts implemented in a CPOE system [10]. Although this intervention had a high impact on prescribing, the hard stop alerts induced clinically significant treatment delays in some patients. Another approach to minimize insignificant warnings recently suggested by Phansalkar et al. [11] is a set of 15 high-priority DDIs, for which alerts should be displayed in all electronic health records.

Automatically provided, workflow-integrated CDS has been shown to be an advantage in successful systems [12]. However, that approach does not consider the burden of excessive automated alerts interfering with the workflow [5]. An on-demand DDI checker might offer an alternative to computer-triggered DDI alerts.

Tamblyn et al. [7] studied on-demand vs. computer-triggered prescription warnings in a user group of 28 primary care physicians. They concluded that both approaches were unable to reduce the prevalence of prescribing problems in primary care.

The clinical information system (CIS; Kisim, Cistec AG, Zurich, Switzerland) of the University Hospital Zurich has implemented an on-demand DDI checker without providing computer-triggered DDI alerts. To our knowledge, the use of an on-demand DDI checker integrated in a CIS for inpatients has not been analyzed so far.

The purpose of this study was to assess the use of the DDI checker by (i) measuring the hospital-wide use of the on-demand checker by both prescribers and consulting pharmacologists, (ii) comparing the number of DDIs identified on-demand with the number that would have resulted by computer-triggering, and (iii) comparing the computer-triggered DDI alerts to patient-specific recommendations by a consulting pharmacist at ward rounds.

2 Methods

2.1 Study Design

The DDI checker was retrospectively analyzed. Data were obtained during 90 weeks, from 12 April 2010 (first activation of the on-demand checker) to 1 January 2012. The local research ethics committee approved the analyses, and patient consent was waived.

2.2 Hospital

The University Hospital Zurich is a teaching hospital covering all specialties, including a total of 850 beds. All data are derived from inpatient care.

2.3 DDI Knowledge Base

Drug–drug interactions were identified using a commercially available knowledge base (galdat/hospINDEX, e-mediat AG, Berne, Switzerland—deduced from ABDA-TA, Werbe- und Vertriebsgesellschaft Deutscher Apotheker, Eschborn, Germany) including comprehensive information on drug classes and agents approved in Switzerland. DDIs increasing and decreasing therapeutic effects are covered as well as adverse drug events [13]. This knowledge base is implemented in the CIS and categorizes the DDIs by six levels of severity (referred to as 'tiering' [14]; cf. Table 1), based on the operational classification of drug interactions (ORCA) [15]. Level 1 DDIs are considered most severe.

Table 1 DDIs retrospectively identified and tiered by the knowledge base in 64,259 inpatients

Level of severity (explanation)	No. of identified DDIs
1. Contraindicated	1,196
2. Contraindicated as precaution	4,674
3. Monitoring or adaptations required	72,046
4. Monitoring or adaptations if risk factors are present	18,827
5. Monitoring as precaution	70,580
6. Usually no action required	1,869
Total	169,192

2.4 Clinical Information System

Since late 2009, inpatient care is managed via CIS on all wards of the University Hospital Zurich except for intensive care units. All medication orders are entered by CPOE. The system offers several CDS functions, involving medication and laboratory data [16]. The knowledge base and front-end of the DDI checker are integrated components of the CIS.

2.5 User Groups

There are two distinct groups of users: (i) the prescribers and (ii) the consultants. The prescribing physicians were categorized on the one hand according to specialty (internists, surgeons, other prescribers) and on the other hand according to professional experience (students and interns, residents, senior physicians). Consultants were non-prescribing pharmacologists and pharmacists.

2.6 DDI Checker

Prescribers and consultants of the University Hospital Zurich including the hospital-associated cantonal pharmacy can independently screen on-demand for DDIs, either during order entry (mode 1), while reviewing the patient chart (mode 2), or before printing prescriptions and reports (mode 3).

In mode 2, the on-demand tool checks the prescribed medication for DDIs within the time frame displayed on screen. Depending on the definition of workflow integration, the studied tool may be considered as integrated, because two mouse clicks within the electronic patient chart are sufficient to start the DDI checker.

The service provided by the checker consists of a tiered list of DDIs identified in the patient's drug orders. The DDIs are sorted by severity level in ascending order, thus displaying the most severe DDIs uppermost. The majority of DDI reports neither suggest alternative therapies nor provide concise, specific management recommendations. The DDI checker and its underlying knowledge base do not consider patient parameters.

Time and mode of activation of the DDI checker, the user name, and the number of identified DDIs were logged. The number of users was calculated by counting any user screening prescriptions for DDIs at least once.

A user could customize the severity level up to which DDIs should be displayed. This limit was logged also. However, an analysis of the logs showed that the default setting (i.e., level 4) was changed by users in less than 1 %. At 'level 4' preset, the four most important levels of severity (levels 1–4) are displayed, whereas reports on DDIs of level 5 and 6 remain hidden. With just one additional mouse click all DDIs (levels 1–6) are listed, tiered by severity.

2.7 Consulting Pharmacist

The impact of a consulting service on DDIs was evaluated in a medical ward by a consulting pharmacist, visiting a total of 922 patients at weekly rounds. The clinical significance of an identified DDI in the context of a patient's condition was taken into account by this consultant. If indicated, the pharmacist recommended a time-displaced administration, intensified monitoring, substitution of a drug agent, dose adjustments, or discontinuation of a specific drug. The pharmacist collected data about recommendations applied by internists in charge.

In some cases the pharmacist also used other knowledge bases in addition to the implemented one and reviewed literature for further analysis of the specific situation. These findings are not represented in the proprietary knowledge base implemented in the CIS (cf. Table 2, 'n.r.').

2.8 Overall Number of DDIs

Drug–drug interactions were retrospectively identified for pairs of concurrently prescribed drugs using the most recent version of the DDI knowledge base available at that time (February 2012). Replacing agents among the same drug class associated with the same DDI were counted as a single prescription (referred to as 'class–class interactions' [17]). Prescriptions for time periods spaced for 24 h or less were merged to avoid overestimated DDI numbers. Changes in dosing were not additionally considered, i.e., were counted as a single DDI.

All DDIs independently identified by prescribers and consultants as a result of the on-demand DDI checker are part of the total number of DDIs retrospectively identified by screening all prescriptions of all inpatients. Further, the DDIs identified by the knowledge base for the medical ward studied in greater detail (cf. Table 2, levels 1–6) result from the same algorithm used to perform the overall analysis and are therefore an inherent part of the total number of DDIs.

2.9 Statistical Analyses

Chi-square tests of independence were used for statistical analysis of frequencies in contingency tables. Differences in the frequencies of on-demand use between residents and other groups of prescribers were analyzed by the Kruskal–Wallis rank sum test. The p levels of 0.05 and less were considered statistically significant. Data analysis and statistical tests were performed using the software EpiData V2.2.1.171 (EpiData Association, Odense, Denmark).

3 Results

3.1 Hospital-Wide Use of the On-demand DDI Checker

Users screened prescriptions 10,828 times (120 checks/week), and a total of 16,553 DDIs were identified on-demand (1.5 DDIs/check). Prescriptions were checked by 653 users, including 644 prescribing physicians (eight checks per prescriber). By far the most frequent users were nine pharmacologists screening for DDIs in preparation for their consulting service, but not personally in charge of prescribing medication (648 checks per consultant). Thus, total use of the DDI checker was higher by consultants (54 %) compared to prescribers (internists 28 %, surgeons 8 %, other prescribers 10 %) (Fig. 1).

Prescribing residents used the tool more often than other groups of prescribers (11.1 checks per resident vs. 4.3 checks per senior physician and 2.4 checks per student or intern; $p < 0.0001$) (Table 3). Among specialty and experience, the number of prescribing users did not significantly differ; however, the frequencies of use were different ($p < 0.0001$).

Surgeons and other prescribers checked mainly during order entry (mode 1), whereas internists predominantly screened for DDIs while reviewing the patient chart (mode 2) ($p < 0.0001$; Table 4).

Physicians in internal medicine obtained higher numbers of DDIs per check (1.7) compared to surgeons

Table 2 Number of DDIs identified by the knowledge base and pharmacist's recommendations in a medical ward

Level of severity[d]	Knowledge base	Ward's consulting pharmacist		Ward's prescribing internists		
	A[a] = Identified DDIs	B[b] = Recommendations	B/A Recommendations/ identified DDIs (%)	C[c] = Applied recommendations	C/A Applied recommendations/ identified DDIs (%)	C/B Recommendations applied by prescribers (%)
1	23	6	26.1	6	26.1	100
2	171	15	8.8	14	8.2	93.3
3	2,866	62	2.2	47	1.6	75.8
4	816	14	1.7	10	1.2	71.4
5	3,998	7	0.2	6	0.2	85.7
6	28	0	0	0	0	–
n.r.[e]	–	24	–	14	–	58.3
Total	7,902	128	1.6	97	1.2	75.8

[a] Number of DDIs identified by the knowledge base

[b] Number of recommendations by a consulting pharmacist to prevent DDIs

[c] Number of pharmacist's recommendations applied by internists in charge

[d] For explanations of the levels of severity, see Table 1

[e] Findings of the pharmacist not represented within the implemented knowledge base

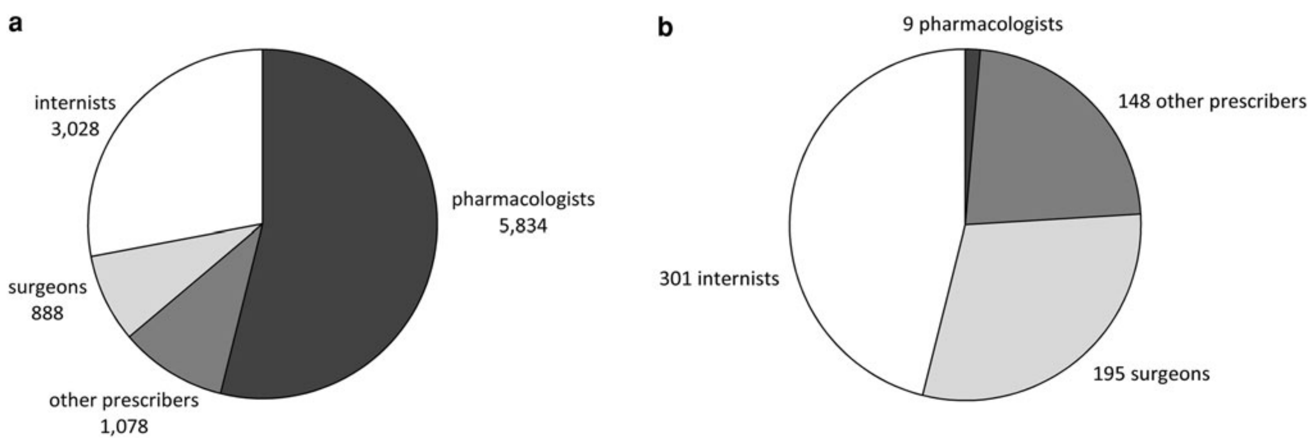

Fig. 1 **a** Number of on-demand DDI checks triggered by prescribers and consulting pharmacologists. **b** Number of prescribers and consulting pharmacologists using the DDI checker

Table 3 Number of checks triggered on-demand, number of prescribers, and average number of checks per prescriber, by position and specialty of prescribers

	All prescribers			Internists			Surgeons			Other prescribers		
	No. of checks	No. of users	No. of checks/no. of users	No. of checks	No. of users	No. of checks/ no. of users	No. of checks	No. of users	No. of checks/no. of users	No. of checks	No. of users	No. of checks/no. of users
Students and interns	342	141	2.4	177	72	2.5	92	44	2.1	73	25	2.9
Residents	4,073	367	11.1	2,426	167	14.5	745	118	6.3	902	82	11
Senior physicians	579	136	4.3	425	62	6.9	51	33	1.5	103	41	2.5
Total	4,994	644	7.8	3,028	301	10.1	888	195	4.6	1,078	148	7.3

Table 4 Number of on-demand DDI checks by selected mode and specialty

	All users	Fraction of total (%)	Internists	Fraction of total (%)	Surgeons	Fraction of total (%)	Other prescribers	Fraction of total (%)	Consulting pharmacologists	Fraction of total (%)
Mode 1[a]	2,262	20.9	738	24.4	689	77.6	829	76.9	6	0.1
Mode 2[b]	7,551	69.7	1,472	48.6	93	10.5	159	14.7	5,827	99.9
Mode 3[c]	1,015	9.4	818	27.0	106	11.9	90	8.3	1	0.0
Total	10,828		3,028		888		1,078		5,834	

[a] On-demand DDI checks during order entry

[b] Checks while reviewing patient charts

[c] Checks before printing prescriptions or reports

Table 5 Hospital-wide top 10 most frequent level 1 and level 2 DDIs identified by the knowledge base

Level of severity	Interacting class 1	Interacting class 2	No. of occurrences
2	Clopidogrel	Proton pump inhibitors	942
1	Potassium supplement	Potassium-sparing diuretics	888
2	QT-prolonging agents	Droperidol, pimozide, sertindole, thioridazine	850
2	QT-prolonging agents	Antiarrhythmic agents	813
2	Clopidogrel	Enzyme inhibitors (CYP2C19)	302
2	Antiarrhythmic agents	Antibiotics	287
2	Levodopa	Dopamine antagonists	150
2	Opioid agonists	Opioid agonists/antagonists	138
2	Neuroleptics	Ethanol[a]	115
1	Statins	Macrolide antibiotics	104

[a] Pharmaceutical formulations containing ethanol as an additive

(0.4 DDIs/check). The number of medication orders for patients in wards of internal medicine and surgery averaged 19.0 and 12.8, respectively.

3.2 DDIs Identified by the Knowledge Base

A total of 1,316,884 prescriptions in 64,259 inpatients (ca. 20 drug orders/patient) were retrospectively analyzed. The proprietary knowledge base implemented in the CIS identified 169,192 DDIs, i.e., tenfold the number identified on-demand. If the knowledge base had automatically triggered all DDI alerts, on an average 2.6 DDI alerts per patient would have been displayed. Restricting the computer-triggered DDI alerts to the four or three highest levels of severity would have resulted in 1.5 or 1.2 alerts per patient, respectively (Table 1). The ten most frequent level 1 and level 2 DDIs identified by the knowledge base accounted for 4,589 DDIs (Table 5).

3.3 Patient-Specific Recommendations by a Pharmacist

On a medical ward, a consulting pharmacist once a week joined internists visiting their patients. If indicated, the pharmacist suggested specific modifications to minimize the risk of potentially harmful DDIs.

The pharmacist made only 128 recommendations for the 922 inpatients visited (0.14 recommendations/patient) (Table 2). In contrast, computer-triggering the DDI checker would have generated 6.3 alerts/patient on this ward (7,902 DDIs/1,263 patients), i.e., the number of alerts would have increased by a factor of 45.

However, in 97 of the 128 cases, these suggestions were applied by the physicians in charge, either as a time-displaced administration (34 % of applied recommendations), intensified monitoring (24 %), substitution of a drug agent (20 %), dose adjustments (13 %), or discontinuation of a specific drug (9 %). These order changes were implemented in 81 % immediately, in 13 % the next day, and in 6 % within a week. Thus, the acceptance of the pharmacist's recommendations according to the decisions made by the physicians in charge of the patient was 76 %.

The fraction of pharmacist's recommendations per number of DDIs identified by the knowledge base correlated with the severity levels ($p < 0.0001$), i.e., the higher the DDI severity according to the tiered knowledge base, the higher was the likelihood of a recommendation by the consultant (Table 2).

4 Discussion

Frequent computer-triggered DDI alerts of low clinical significance induce alert fatigue and therefore minimize the impact of CDS systems [5, 6]. Offering a DDI checker as an on-demand service is a strategy to avoid alert fatigue. Surprisingly, this DDI checker integrated in the CIS of a teaching hospital was predominantly used by the few consulting pharmacologists. In contrast, we observed a quite limited on-demand use by the large number of physicians in charge of prescription. However, the acceptance of a patient-adapted service to avoid DDIs provided by a consulting pharmacist at ward rounds reached 76 %.

All professionals using the on-demand tool received identically presented DDI lists, tiered by severity level, in the majority of the DDI reports lacking specific management recommendations. On the one hand, inexperienced prescribers may feel uncertain about modifying established medication orders, particularly in the absence of recommendations for alternative therapies. On the other hand, senior physicians may disagree with the clinical significance of the reported DDIs because patient parameters and context were not considered by the DDI checker. Nevertheless, the high use of the on-demand DDI checker in the consulting pharmacologists group suggests that these specialists found the tool convenient for generating DDI lists and supporting the preparation of ward rounds and consultations.

The fact that internists found more DDIs per check than surgeons is in line with other studies [18], presenting higher numbers of prescribed drugs per patient in wards of internal medicine, similar to our findings. Internists predominantly screened for DDIs while reviewing the patient chart (mode 2) in order to overview the concurrent drug therapies frequently administered to multimorbid patients.

As early as 1977, Morrell et al. [19] investigated an automated service involving a computer in the hospital pharmacy sending reports to prescribers when DDIs had been detected. The authors stated that the service was most useful for medical students and interns, because of their inexperience, their direct engagement in patient care, and the importance of drug therapy in medical patients. However, the survey of the users revealed the "unduly repetitive" [19] nature of the reporting service as the major problem, a finding that is still valid because of the poor signal-to-noise ratio of comprehensive DDI information [20, 21].

Despite tremendous improvements in hardware and software seen in recent years, clinicians are frustrated by the dominance of false positive DDI warnings due to the shortcomings of the available knowledge bases. There are limited opportunities to safely turn off frequently overridden alerts [22]. Successful strategies to improve the specificity may require more sophisticated algorithms, e.g., by considering renal insufficiency, or upper dose limits for statins deduced from pharmacokinetic studies [23, 24]. Although minimizing the number of alerts is an approach to increase the specificity, DDI compendia show little consensus about the most severe DDIs [25]. However, an expert panel recently suggested a set of 15 important DDIs for which all CIS should display alerts [11].

Limitations of our study include lack of a sensitivity analysis of the knowledge base implemented to identify DDIs. Though a comprehensive knowledge base should achieve a high sensitivity, 24 recommendations by the pharmacist to prevent DDIs were not included in the knowledge base (cf. Table 2). Worth mentioning are 7 of these 24 recommendations concerning liquid paraffin as a laxative interfering with fat-soluble agents; yet, lipophilicity is not represented within the knowledge base. The pharmacist's recommendations have not been validated by another specialist. Further, it is possible that some of the issues addressed by the pharmacist had already been identified on-demand by a prescriber; however, this was not verifiable in this retrospective analysis. Whether critical DDIs might have been missed if users infrequently searched for DDIs remains unknown because the checker did not log severity levels and identification numbers of interacting orders required for such an analysis. The comparison of the computer-triggered DDI alerts with the pharmacist's recommendations is based on data from DDIs found in a group of 922 medical patients. That is a modest sample size and in other specialties than internal medicine numbers of automated alerts could differ. Nevertheless, our data are consistent with previous reports, observing limited sensitivity and poor specificity of knowledge bases [26, 27].

Developing algorithms that provide patient-specific recommendations is a major challenge. Most implementations neither sufficiently address patient conditions nor generate detailed recommendations. Further research is necessary to adequately support prescribing physicians. Decisions taken on DDIs in the presence of a pharmacist consultant during clinical visits may or may not be the gold standard. However, they do represent a quality-controlled approach to the management of DDIs, documenting a quite limited need for changing orders, i.e., in less than 10 % of the patients (79 of 922, on the evaluated ward). The acceptance of 76 % of the pharmacist's recommendations and their immediate implementation by the prescribing internists in 81 % underline the practicability and clinical significance of the pharmacist's service.

The pharmacist's recommendations correlated with the levels of severity provided by the knowledge base. Categorizing DDIs by severity is necessary but not sufficient to solve the problem [7, 25, 28]. Drug combinations associated with DDIs considered severe are sometimes ordered by prescribers *because of* a well-known DDI and not *despite* it. For example, the most frequent level 1 DDI observed was related to the treatment of hypokalemia by ordering potassium-sparing diuretics and potassium supplement (cf. Table 5), generating a DDI report warning against the risk of hyperkalemia [18]. Thus, before reporting a DDI, the condition of the patient should be taken into account. Such concepts may offer promising strategies to improve the specificity of computer-triggered alerts [11, 20, 27, 29].

Among the 10 most frequent level 1 and level 2 DDIs identified by the knowledge base (cf. Table 5), the "prescription" ethanol needs further explanation. Ethanol may be used in pharmaceutical formulations as an additive. Several distinct drugs containing ethanol are involved in the 115 interactions identified by the knowledge base. Since these drugs contain only small quantities of ethanol, the sedative effect described for the concurrent administration with neuroleptics may be less significant than suggested by the severity level 2. Triggering warnings for DDIs of little clinical significance would contribute to alert fatigue.

Drug–drug interactions reports should be concise, user-friendly, and customizable [29]. Personal options such as "remind me in one week" and "don't show this message again" could be part of this approach. In order to attract prescribers, DDI reports providing alternative management recommendations have been advocated [30].

Customer-adapted tailoring of DDI alerts is of importance as documented by the highly diverse frequency of use by prescribers and consultants. A "one fits all" DDI warning system may not meet the needs of all user groups: On the one hand, consultants are interested in a system providing high sensitivity, and on the other hand, prescribers are interested in patient-specific support including detailed advice [9].

5 Conclusions

The on-demand DDI checker was popular with the pharmacologists. In contrast, prescribing physicians used the tool infrequently. However, prescribers accepted professional advice to avoid DDIs, as documented by the substantial impact of patient-specific recommendations. The prescribers' limited on-demand use indicates the necessity for developing improved safety concepts, tailored to suit these consumers. Thus, different approaches may have to satisfy the needs of different target groups.

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Author Contributions All authors contributed to the conception and planning of the work, analyzed and interpreted data, contributed to the drafting and critical revision of the manuscript, and all authors approved the final submitted version.

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