Clinical Decision Support Systems: a systematic literature review of drug-drug interaction alerts
# Table of Contents

Summary .................................................................................................................................................. 3
Acknowledgements ................................................................................................................................... 4
Conflict of interest .................................................................................................................................. 4
Abbreviations ........................................................................................................................................ 4
Terms ..................................................................................................................................................... 5
Introduction ........................................................................................................................................... 5
  Aim ....................................................................................................................................................... 8
  Objectives .......................................................................................................................................... 8
Methods ................................................................................................................................................ 8
Results .................................................................................................................................................. 9
Discussion ............................................................................................................................................. 17
  Limitations ......................................................................................................................................... 18
  Clinical implications, practical and research recommendations ..................................................... 19
Conclusions ........................................................................................................................................... 19
References ............................................................................................................................................. 20
Clinical Decision Support Systems (CDSS) integrate a medical knowledge and patient data to produce a computerized case specific advice. A type of such advice are drug-drug interaction (DDI) alerts, expected to reduce inappropriate co-prescription rates and medical errors. However reported evidence on efficacy of such systems is limited.

The aim: to perform a systematic evaluation of CDSSs on effectiveness to report DDI cases and improve prescriber/patient outcomes.

Objectives: (1) to analyze principles of DDI alerts and reporting; (2) review quality of CDSS alerts of DDI; (3) to present the findings; and (4) to provide relevant recommendations.

Methods: an online literature search was conducted on Medline using key words „Clinical Decision Support Systems“ and „Drug Interaction“. The outcomes of interest were changes in prescription, patient outcomes and data on specificity/sensitivity/positive predictive value (PPV) of DDI alerts. Exclusion criteria were no full text available, other (non-CDSS) alert systems, non-prescription interventions, no comparator used for outcome assessment, qualitative studies and opinion surveys.

Results: the search returned a total of 490 publications: n=357 in PubMed, n=44 in Cochrane Library, and n=89 on manual search. Following the review 476 articles were excluded, leaving 14 studies of interest. The eligible studies were divided into 2 groups: the 1st group of studies (n=6) addressed the benefits of DDI alerts on prescriber/patient outcomes, and the 2nd (n=8) group reported PPV or sensitivity/specificity values. There was a variation among prescriber outcome measures among the 1st group author teams, and comparable quantitative outcome data was not possible to produce. Half of the 1st group studies reported a statistically significant beneficial effect from DDI alert on prescriber's behavior (n=3.50%), while the other half of the studies reported none (n=3.50%). One study (16.7%) evaluated patient outcomes, and a significant benefit was observed. One study (16.7%) was stopped prematurely due to safety concerns. The reported PPV of DDI alerts was very low reaching up to 10% in most studies. Advanced CDSS have demonstrated higher PPV compared to the basic vendor software (14.8% vs 9.9%, p<0.05). Reported DDI alert sensitivity ranged between 9%-96%. Reported specificity also depended on the software vendor (29-94%), and was higher in advanced CDSS.
Conclusions: Current CDSSs do not meet the prescribers’ needs. The evidence on patient outcome is lacking, and further studies are needed to establish their role in clinical care.

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Conflict of interest

I declare no conflict of interest related to this work.

Abbreviations

BICS - Brigham Integrated Computer System;
CDSS - Clinical Decision Support Systems;
CPRS - Computerized Patient Record System;
DDI - Drug-drug interaction;
NSAID - Non-steroid anti-inflammatory drugs;
PPV - Positive predictive value;
R - Response;
RCT - Randomized controlled trial;
VISTA - Veterans Information System Technology Architecture;

USA - United States of America.

**Terms**

The Final Master’s Thesis ‘Clinical Decision Support Systems: a systematic literature review of drug-drug interaction alerts’ was prepared during the period of October, 2017 – April, 2018.

**Introduction**

Contemporary developments of clinical medicine rely on modern advances in tools and techniques that support the healthcare system workers in daily practice and decision making. Among such tools are Clinical Decision Support Systems (CDSS), which are known as computerized knowledge systems which use integrated patient data to generate a patient-specific advice (1). These systems integrate a medical knowledge base, patient data and an inference engine to produce a case specific advice at the point in time the decisions are made. Introduction of such systems has been shown to improve patient outcomes and reduce the cost of care (2) (3). They are comparable to implication of artificial intelligence into medical field with potential to revolutionize the future healthcare, medical teaching and practice. However to this date their use and applications are still limited (4) (5). These systems are capable of performing the following functions (6):

- Administrative: support of clinical coding and documentation, procedure/referral authorization.
- Management: storing clinical details (e.g. research/therapeutic protocols, tracking referrals/follow-ups, preventive care).
- Control: monitoring medication orders, avoiding duplicate or unnecessary tests (cost saving measures).
- Decision support: establishment of clinical diagnosis/treatment plan, promoting best clinical practice or condition-specific guidelines, population-based management.

Medication consumption is constantly increasing with numerous multi-drug treatment prescriptions dispensed on a daily basis, therefore possibility of drug-drug interaction (DDI) is one of the most clinically relevant issues encountered in practice. A DDI is defined as a clinically significant physiological alteration in the exposure and/or response to a drug that has occurred as a result of co-administration of another drug (7). Exposure to potential DDI can cause preventable drug-related harm and is a serious medical error (8). To aid prescription process CDSS may include alerts, reminders, order
Clinical Decision Support Systems: a systematic literature review of drug-drug interaction alerts

sets and drug dose calculations. DDI alerts are of particular interest as their nature is very suitable for highly efficient automated interventions performed by computerized CDSS (9). Many electronic prescription and medication information systems include some form of CDSS alerting regarding drug dosing, duplicate therapy, and potential DDI. DDI alerts most commonly appear during the prescription medication order entry or at dispensing/verification process at the pharmacy. CDSS-assisted DDI checking is estimated to yield a return on time investment of almost 10 years (2).

Principles of DDI alerts and reporting in CDSS. The DDI database integrated into the CDSS is usually linked to a prescription system of a healthcare institution or pharmacy (6). It provides automatic alerts during drug prescription process in cases of potentially dangerous or contraindicated drug combinations. For optimal and advanced use CDSS should be implemented into a local/national database, which allows access to patient specific data such as age, sex, height, weight, blood test results, and the medication a patient is already using (10). Through certain software algorithms an alert could then be triggered or not, providing a relevant patient specific warning rather than alerting on each potential DDI by default. The types of DDI alerts range from non-intrusive reminders to mandatory “hard-stop” prescription warnings (the prescriber is required to abandon the prescription or prescribe an alternative drug) (11). Some providers use color coding for the alert messages to reflect the urgency of the warning by the CDSS: e.g. red – very important information (avoid combination), yellow – important information to consider (dose adjustment recommended), white – information only with no action required (12). Higher alert acceptance and user compliance rates are observed when only high severity DDI alerts are interruptive in nature, otherwise they only increase tendency to ignore, work around or override them (11) (13). Certain providers offer an on-demand rather than computer triggered DDI alerting mode as a solution to reduce existing computerized prescribing problems, however in effectiveness such systems have not shown any advantages (14) (15). Prescribers response to DDI alerts may be of passive nature including situations where DDI alerts can be completely missed or ignored (message pop-up on prescription screen), or active – acknowledgement (a button press to accept a potential DDI), overriding (sometimes with a request to type in a reason/explanation for combination prescription) or „hard stop“ prescription orders (abandon prescription/prescribe alternative) (11). Although „hard stop“ DDI alerts significantly reduce inappropriate co-prescription rates, they have been shown to be problematic at times in clinical practice and are rarely used, except for clinical trials (16).

Quality of CDSS DDIs alerts. There is no agreed standard to define qualitative performance of CDSS. However, as other computerized software it can be described by objective performance characteristics and a degree of user satisfaction. There is a substantial variability in DDI alerting performance across electronic prescribing and pharmacy software systems published in the literature (17) (18) (19) (20) (21). Based on current publications and reviews, degree of excellence in CDSS performance is very low, and
improving the state-of-the art of CDSS faces a few considerable challenges. Alerts of ambiguous or low clinical relevance are a major limitation of these systems and have caused considerable clinical frustration and user dissatisfaction with reported alert override rates consistently exceeding 90% (5) (22) (23) (24) (25). One of the major contributing factor to the latter phenomenon is a lack of guidelines and approved standards for determining clinical relevance of DDIs, and without such guidance DDIs are often inappropriately extrapolated to other drugs within the same therapeutic/pharmacologic class (26) (27). Also, many „possible“ DDIs lack high quality evidence to support their existence, controlled clinical studies in relevant populations are scarce, as well as random cases are underreported and often lack information (26) (28) (29). Commercially available DDI databases in an effort to reduce legal liability, include almost all possible DDIs, including those that confer extremely low risk to exposed patients leading to excess of irrelevant and non-specific alerts and consequent alert fatigue (30). Multiple alerts of low importance create disturbances in already burdened healthcare professionals work flow and may even be source of clinical errors rather than a preventive mean from them (31). Another issue with DDI alert generation is database inconsistencies among different software providers: certain DDIs are ranked as high risk by one provider while at the same time are considered low risk by the other CDSS (32). Research and investigation of DDI in CDSS is usually focused on how CDSS intervention influences prescribing behavior and patient outcomes. These studies include quasi-experimental designs (uncontrolled or controlled before-and-after studies, interrupted time series) and randomized controlled trials (3) (11) (16) (31) (33) (34) (35). Published reviews report that the use of CDSS reduces healthcare costs and time consumption, improves patient safety, and prescriber practice (2) (36) (37) (38) (39). Yet, evidence of improved patient outcomes has been limited (36) (39) (40). Quantitative parameters describing effectiveness and specificity of CDSS DDI alerts are reviewed in more detail along with the findings of this study in the discussion section below the results. Alternative CDSS research strategies include qualitative research methods to provide a deeper understanding of subjective aspects of the interaction among healthcare professionals, patients and the electronic CDSS interface. Generally CDSS users (physicians) expressed pronounced irritation due to abundance of irrelevant alerts, which often led to ignore them (4) (25). Despite being aware of the fact that the decision support system contributes to safer and more effective treatment of patients, prescribers were dissatisfied with the usability of this tool, as well as pointed out some technical barriers and limitations (36) (41). Based on the current overview, current CDSS DDI alerting appears not to meet the prescribers’ needs, and its role in improving healthcare practice and patient outcomes is currently unclear.
Aim

The aim of this study is to perform a systematic evaluation of CDSSs on effectiveness to report DDI cases and improve prescriber/patient outcomes.

Objectives

1. To analyze principles of DDI alerts and reporting.
2. To conduct a literature review regarding quality of CDSS alerts of DDI.
3. To present the evidence-based findings on effectiveness of DDI alerts to improve prescriber and patient outcomes.
4. To provide relevant practical recommendations regarding CDSS and DDI alerts based on current scientific data and research.

Methods

The PRISMA guidelines on the conduct and reporting of systematic reviews was applied (42).

Protocol and information sources: A search of studies published between January 1976 and January 2018 addressing CDSS and DDIs was conducted in Medline accessed through PubMed, and The Cochrane Library. Key words included „Clinical Decision Support Systems“ and „Drug Interaction“ (no quotes used). Expanders applied included „Apply related words“ and „Search within the full text of the articles“. Besides electronic database literature search, additional potentially relevant studies were identified via manual searching (references of published articles, related articles suggested by electronic search engines).

Eligibility criteria and study selection: Only studies published in English were further included in the analysis. Studies must have evaluated the impact of automatic computer-derived DDI alerts and notifications at the time of medication prescription. Studies were included if they analyzed the outcomes from the intervention (DDI alert) by comparing to either a pre-test period and/or a control group to determine alert effectiveness. The outcomes of interest were changes in prescription (cancelling order or prescribing another appropriate drug), and/or patient outcomes (clinical evidence of potential/actual harm or benefits to direct welfare of the patient), and/or data on specificity/sensitivity or positive predictive value (PPV) of DDI alerts. A two-staged approach was used for review process. In the first stage all titles and abstracts were screened for relevance. Items not meeting inclusion criteria and duplicates were removed. In the second stage of review process articles potentially meeting the inclusion criteria were retrieved and reviewed regarding final inclusion.
eligibility. Following full-text review final number of studies meeting the inclusion criteria was identified.

**Exclusion criteria:** Articles were excluded if studies were only in abstract form with no full text available, involved other clinical information systems (hospital documentation and information portals not linked to CDSS), addressed non-prescription interventions (imaging, blood test orders, etc), if no comparator was used for outcome assessment, outcomes measured were different from investigated. Qualitative studies and opinion surveys were also excluded.

**Data collection:** Data about study setting, design, participant characteristics, interventions and outcomes was obtained from each study by one investigator.

**Analysis:** A number of eligible studies of interest was eventually identified. Reported outcomes and endpoints varied among studies. Comparable quantitative data was insufficient for meta-analysis, therefore the findings were grouped and reported in a narrative approach. Results were categorized as either statistically significant (beneficial impact on prescription/patient outcomes) or of no statistically significant impact (include no statistical analysis performed). Effectiveness of CDSS was illustrated by reported PPV by study authors or calculated manually if unreported but the published data allowed these calculations.

### Results

Literature review on principles of DDI alerts/reporting (*Objective 1*) and quality assessment (*Objective 2*) are presented in the introduction, and further addressed in the discussion sections.

Comprehensive literature search conducted on February 14, 2018 identified a total of 490 published items: 401 on electronic database search (n=357 in PubMed, and n=44 in Cochrane Library), and 89 on manual search. Following the first stage screening 409 articles were removed: 58 duplicates, 348 irrelevant titles/abstracts, 2 missing or inaccessible full text and 1 published not in English language. A total of 81 articles were eligible for the second stage of review. After second stage full text revision 14 studies were selected that are relevant and correspondent to study objectives. The flow chart of the study selection process is presented below in *Figure 1*. Detailed results of the literature search are presented as a supplementary data (*Annex 1*).
Clinical Decision Support Systems: a systematic literature review of drug-drug interaction alerts

Figure 1. A flow chart of the study selection process.

Consequently the eligible studies were divided into 2 groups (Figure 2). The first group of studies (n=6) aimed to address the benefits of DDI alerts on prescriber/patient outcomes, and the second group (n=8) reported objective evidence of DDI alert relevance (PPV or sensitivity/specificity values).
Clinical Decision Support Systems: a systematic literature review of drug-drug interaction alerts

Figure 2. Overview of the selected studies. DDI – drug-drug interaction.

The studies investigating efficacy and benefits of DDI alerts (Table 1) in clinical setting were published between the years 2005 and 2012, and predominately originate from the United States of America (n=5, 83.3%) (3) (11) (16) (33) (34). One study (16.7%) was conducted in Europe (Italy) (31). All investigations were carried out at the hospital in-patient environment. No eligible studies addressed CDSS derived DDI concerns or effectiveness in outpatient setting. The patient population contained adult individuals in all reported studies. The targeted CDSS users (prescribers) were either solely physicians/clinicians (n=2, 33.3%), physicians/nurses (n=1, 16.7%), or physicians/nurses/pharmacists (n=2, 33.3%). In one study (16.7%) prescribers were not specified. CDSS manufacturer details and other study characteristics are summarized in Table 1. Half of the studies (n=3, 50%) were of retrospective design. All authors investigated the effect of the intervention alert on at least one outcome measure of prescriber’s behavior. There was a variation among prescriber outcome measures applied by different author teams, therefore comparable quantitative outcome data was not possible to produce. Three studies (50%) assessed order cancellation rate in response to alerts, 1 (16.7%) – inappropriate prescribing rate, 1 (16.7%) – alert override rate, and 1 (16.7%) – alert adherence and incidence of potential DDIs (with no significant statistical calculations provided). Half of the studies reported a statistically significant beneficial effect from DDI alert on prescriber’s behavior (including one study demonstrating adverse consequences with consequent early termination due to prescription delays (16)), while the other half of the studies reported none. One study did not report neither general DDI alert adherence nor inappropriate prescription rate, and no statistical analysis was performed (31). However, they have observed an increase in prescribing errors (number of potential DDIs) in certain clinical areas after DDI alert implementation, while a positive trend toward reduction of such errors was observed in the others. A definitive conclusion whether DDI has a proven beneficial impact on prescriber outcomes cannot be
drawn due to inconsistent prescriber outcome measures among investigators, and very limited number of eligible studies identified which already demonstrate diverging results (50:50 benefit/no-benefit ratio).
## Clinical Decision Support Systems: a systematic literature review of drug-drug interaction alerts

<table>
<thead>
<tr>
<th>First author, year</th>
<th>Country</th>
<th>Patient population</th>
<th>Prescribers/CDSS users</th>
<th>CDSS</th>
<th>Study design</th>
<th>Study type</th>
<th>Comparator</th>
<th>Alert trigger(s) Alert responses (R)</th>
<th>Outcomes and Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peterson, 2005 USA</td>
<td>Adult n=3718</td>
<td>Physicians/nurses</td>
<td>BICS; Partners Healthcare</td>
<td>Prospective</td>
<td>Repeated-measures design; usual prescription vs CDSS-assisted time periods</td>
<td>Pretest</td>
<td>Inappropriate psychotropic medication prescription. 1. Prescribe suggested substitution. 2. Proceed with original order. 3. Cancel order.</td>
<td>Inappropriate prescribing rate 10.8% vs 7.6%, p&lt;0.001</td>
<td>1. Length of in-hospital stay; 2. In-hospital falls; 3. Number of days of altered mental status. 1.4 (2.6) vs 4 (2.6), p=0.43 2. 0.28 vs 0.64, p=0.001 3. 20.9 vs 21.3, p=0.17</td>
</tr>
<tr>
<td>Lin, 2008 USA</td>
<td>Adult n=2/a</td>
<td>Physicians/nurses</td>
<td>CPRS VISTA</td>
<td>Retrospective</td>
<td>1-group pretest-posttest: data from 2001 and 2006</td>
<td>Historical cohort</td>
<td>High severity DDI. 1: cancel or continue order (requires override). 2: alert override.</td>
<td>Alert override rate 87.9% vs 87.1%, p=0.85</td>
<td>n/a</td>
</tr>
<tr>
<td>Paterno, 2009 USA</td>
<td>Adult n=2/a</td>
<td>Clinicians</td>
<td>BICS; Partners Healthcare</td>
<td>Retrospective</td>
<td>Posttest-only with nonequivalent control: 2 medical centres</td>
<td>Control</td>
<td>DDI according to severity level (1): 1: life-threatening; 2: must cancel order; 2: less serious; 3: must cancel or override; 3: least serious (information); 4: no action required. 1: prescribed randomized to silent or active DDI alert. 2: alert override.</td>
<td>Orders cancelled in response to alert 1: 34% vs 100%, p&lt;0.001 2: 11% vs 29%, p=0.001 3: n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Strom, 2010 USA</td>
<td>Adult n=2/a</td>
<td>Clinicians</td>
<td>Sunrise Clinical Manager (Eclipsys Corp.)</td>
<td>Prospective</td>
<td>RCT: clinicians randomized to silent or active DDI alert</td>
<td>Control</td>
<td>Co-prescription of trimethoprim-sulfamethoxazole and warfarin. 1: cancel order. 2: alert override.</td>
<td>Orders cancelled in response to alert</td>
<td>13.5% vs 57.2%, p&lt;0.001</td>
</tr>
<tr>
<td>Strom, 2010 USA</td>
<td>Adult n=2/a</td>
<td>Physicians/nurses</td>
<td>Sunrise Clinical Manager (Eclipsys Corp.)</td>
<td>RCT: prescribers randomized to silent or active DDI alert</td>
<td>Control</td>
<td>Co-prescription of NSAID and warfarin. 1: cancel order. 2: alert override.</td>
<td>Orders cancelled in response to alert</td>
<td>28% vs 25%, p=0.001</td>
<td>n/a</td>
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<td>Polidori, 2012 Italy</td>
<td>Adult n=2/a</td>
<td>Not specified</td>
<td>Sunrise, Eclipsys</td>
<td>Retrospective</td>
<td>1-group pretest-posttest: before and after 'alert acknowledgement function introduction'</td>
<td>Pretest</td>
<td>Potential DDI. 1: mandatory alert override. 2: alert override.</td>
<td>1. Alert adherence. 2. Incidence of potential DDIs increased in 7 of 8 areas, decreased in 1. Decreased in 4/8 areas, increased in 4/8 areas</td>
<td></td>
</tr>
</tbody>
</table>

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Table 1. Studies on efficacy and benefits of DDI alerts in clinical environment: key characteristics and findings. CDSS—clinical decision support system, USA—United States of America, n/a—data not available (not provided by authors), RCT—randomized controlled trial, NSAID—non-steroid anti-inflammatory drugs.

1. Brigham integrated Computer System.
2. Of the decrease in nonrecommended drug use, 97% was attributable to reduced prescribing of meperidine in both intramuscular and intravenous forms.
3. Median (interquartile range).
4. Number per 100 patient-days.
5. Computerized Patient Record System (CPRS) component of the larger Veterans Information System Technology Architecture (VISTA).
7. Not captured for control site, therefore were not compared.
8. Adjusted odds ratio: 0.12; 95% confidence interval: [0.045-0.33];
9. Intervention resulted in delay in ordering trimethoprim/sulfamethoxazole even in cases where benefits were considered to outweigh the risks were considered and potential for harm by having a control group, therefore the study was terminated early.
10. 11.4/64 vs 154/560, adjusted odds ratio of inappropriate ordering: 3.22 (95% CI 0.69 to 2.16).
11. No significant calculations provided by authors.
Only one (16.7%) of 6 studies has additionally evaluated the effect of DDI alerts on patient outcomes, demonstrating that there is some beneficial effect of alert implementation: a significant reduction of in-hospital falls related to co-administration of 2 or more psychotropic drugs to geriatric patients was observed after DDI alert introduction, however other patient outcomes (length of hospitalization or number of days of altered mental status) remained unchanged (3). One study with a potential to address bleeding complication rates related to co-prescription of trimethoprim-sulfamethoxazole and warfarin was stopped prematurely due to safety concerns by “hard-stop” DDI alert delaying or preventing the patients from required treatment in cases where such co-prescription was necessary (34). There were no other studies identified to report DDI related patient outcome measures, however such outcomes were reported with other drug-related CDSS alerts (drug-condition or drug-allergy interaction), which are irrelevant to this review (36) (38) (39).

There were 8 studies on CDSS reporting data on objective relevance of DDI alerts (PPV or sensitivity/specificity) (5) (9) (10) (15) (43) (44) (45) (46). Detailed information on these studies are presented in Table 2. Two (25%) studies originated from the USA, and 6 (75%) from Europe (The Netherlands and Switzerland). Software vendors were unreported in USA studies. Only 1 study (12.5%) was of prospective design (10), the remainder (n=7, 87.5%) were based on retrospective data analysis. The number of alerts analyzed by authors was either not provided or varied between 365 and 16643. Two studies did not provide the PPV, however calculations were possible based on supplied data. The PPV of DDI alerts was extremely low reaching up to 10% in most studies. Higher reported PPV values by Silverman et al are applicable for separate drugs only (PPV 71% for Theophylline and 60% for Quinidine DDI interactions), and did not represent the general trends of PPV 0-41% for remainder of drugs (45). Advanced CDSS that integrate laboratory and clinical patient data into DDI alert generation have demonstrated significantly higher PPV compared to the basic vendor software (14.8% vs 9.9%, p<0.05) (10). Reported DDI alert sensitivity was in a broad range of 9%-96%. Despite high sensitivity reported by some authors, current CDSS cannot be relied on due to particularly low PPV (9) (46). The data on DDI alert specificity was unavailable and not provided by majority of the authors teams (not reported in 6 (75%) out of 8 publications). Reported specificity was again dependent on the software vendor (29-94%), and was higher in advanced CDSS (43) (46).

Beeler et al made an interesting insight in his investigation: computer triggered DDI check generated approximately 45 times more alerts than would do a specialist trained pharmacist for the same clinical scenarios (15). Compared to other available types of CDSS alerts, DDI alerts appear to be the least relevant ones, while the best PPV (34.1%-73.3%) was reported in drug-lab interactions (10).
<table>
<thead>
<tr>
<th>First author, year</th>
<th>Country</th>
<th>Patient population</th>
<th>Prescribers/CDSS users</th>
<th>CDSS</th>
<th>Study design</th>
<th>Number of alerts</th>
<th>PPV (%)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
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<tbody>
<tr>
<td>Silverman, 2004</td>
<td>USA</td>
<td>Pediatric/adult</td>
<td>Physicians/pharmacists</td>
<td>n/a&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Retrospective</td>
<td>16643</td>
<td>0-71&lt;sup&gt;2&lt;/sup&gt;</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Cash, 2009</td>
<td>USA</td>
<td>Pediatric</td>
<td>n/a</td>
<td>n/a&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Retrospective</td>
<td>n/a</td>
<td>1.4</td>
<td>n/a</td>
<td>n/a</td>
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<td>Van der Sijs, 2010</td>
<td>The Netherlands</td>
<td>n/a</td>
<td>Pharmacists</td>
<td>TPM (2.8.2), Zamicom (2006-1), Chipsoft (4.8 FP), Centrasys (1.20 SP1), Medicatie/EVS (2.41), Theriak (3.4.3)</td>
<td>Retrospective</td>
<td>n/a</td>
<td>n/a</td>
<td>38-79&lt;sup&gt;3&lt;/sup&gt;</td>
<td>29-94&lt;sup&gt;3&lt;/sup&gt;</td>
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<td>Doormaal, 2010</td>
<td>The Netherlands</td>
<td>Adult</td>
<td>Pharmacists</td>
<td>Medicator (iSOFT)</td>
<td>Retrospective</td>
<td>365</td>
<td>12</td>
<td>96</td>
<td>91</td>
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<td>Fritz, 2012</td>
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<td>Adult</td>
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<td>Prospective</td>
<td>743</td>
<td>5.7-8&lt;sup&gt;4&lt;/sup&gt;</td>
<td>9.1-87.9&lt;sup&gt;3&lt;/sup&gt;</td>
<td>n/a</td>
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<td>Zorina, 2012</td>
<td>Switzerland</td>
<td>n/a</td>
<td>Physicians</td>
<td>CDSS MediQ, ID PHARMA CHECK</td>
<td>Retrospective</td>
<td>1759/1041</td>
<td>1.6&lt;sup&gt;5&lt;/sup&gt;</td>
<td>70.6-72.4&lt;sup&gt;3&lt;/sup&gt;</td>
<td>n/a</td>
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<tr>
<td>Eppenga, 2012</td>
<td>The Netherlands</td>
<td>Adult</td>
<td>Pharmacists</td>
<td>Centrasys (iSOFT), Pharmaps Medicatiebewaking PLUS</td>
<td>Prospective</td>
<td>2607/2256&lt;sup&gt;3&lt;/sup&gt;</td>
<td>9.9-14.8&lt;sup&gt;3&lt;/sup&gt;</td>
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<td>n/a</td>
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<td>Beeler, 2013</td>
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<td>Physicians/Pharmacists</td>
<td>Galdat/hospINDEX</td>
<td>Retrospective</td>
<td>7902</td>
<td>1.6&lt;sup&gt;5&lt;/sup&gt;</td>
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</tr>
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</table>
Clinical Decision Support Systems: a systematic literature review of drug-drug interaction alerts

Table 1. Studies reporting data on effectiveness of CDSS DDI alerts. CDSS – clinical decision support system, PPV – positive predictive value, USA – United States of America, n/a – data not available (not provided by authors).

1 Computerized prescriber order entry integrated in institutional computer system with CDSS, software vendor not provided by authors;
2 Depends on specific drug;
3 Depends on software vendor;
4,5 Positive predictive value calculated for the review and defined as the quotient of the number of advice/interventions to prevent a possible adverse drug event and the total number of alerts generated: $^4$(n=3/53) - (n=29/362); $^5$n=47/2866.
Discussion

DDI alerts are reported to be both – the most prevalent and the most frequently overridden or ignored drug safety alerts by CDSS users (47). While CDSS DDI alerts have a potential and are designed to decrease prescribing errors, we found no significant evidence to support beneficial effect of this type of alerts on patient outcome measures, which is one of the most important findings in this study. Similar conclusions were drawn by other reviewers’ teams (40) (48). Such absence of patient outcome evidence related to DDI alerts over decades of CDSS research may be explained by difficulty to investigate and attribute the outcome of interest to the effect of potential/definite DDI: e.g. incidence of geriatric patient falls may be related to psychotropic drug prescription but also may be a result of multiple environmental and other factors. Such studies of DDI reporting although not impossible to conduct, appear to be very time consuming, lack reliable objective measures, as well as include a number of potential confounding factors, and are very likely to yield negative results which would be difficult to publish. Drug-condition or drug-allergy interactions are therefore more favorable for patient outcome research (e.g. QT interval prolongation on electrocardiogram as an effect of QT interval prolonging drug prescription, anaphylactic reaction due to medication, etc.).

The current evidence base does not show a clear indication that DDI alerts are indeed effective on modifying prescribers’ behavior and avoiding prescription errors. While some studies have shown to improve these outcomes, there were a couple which reported none, and one study has even presented contradictory findings with potential for increase of medical errors in some clinical areas (31).

PPV is known to be a gold standard for all diagnostic tools in medicine, and is a desirable, if not mandatory, scientific finding. However, few authors report PPV of CDSS DDI alerts or enough data for its computation, which is an unexpected finding. Reported PPVs are below or near 40%, which is of low statistical value. These findings are in keeping with other authors’ data presented in their CDSS review publications (41) (49). While computer-based CDSS appear as a potentially highly effective method to prevent incidence of deleterious effects of DDI, low PPV of DDI alerts retards CDSS from being a reliable tool in daily practice. The broad range of DDI alert sensitivity is probably attributable to the differing level of DDI significance employed by different vendors and applied in different institutions: increasing the types and numbers of alerts likely increases the false positive rates of the overall and individual alerts (5). In real life it is difficult to balance DDI alerts: in many in-patient hospital settings many medications known to cause significant DDIs are often used together on a routine basis (e.g. sedatives and anesthetics in critical care units and operation theatres). The most frequent reasons for DDI alert override given in the literature are as follows: (a) no clinical importance of alert, (b) no alternative prescriptions available and benefits outweigh the risks, (c) potential DDI
can be managed by appropriate monitoring; (d) dose adjustment available, (e) the patient had previously tolerated the medications (9) (13) (50). Abundance of irrelevant alerts often lead to subsequent “alert fatigue” when important alerts are being ignored along with unimportant ones. Most CDSSs allow to turn off specific DDI warnings depending on interaction severity (high/average/low risk) thus reducing the number of false positive alerts and firing an alert only when the severity of an interaction is high (13). However, lowering sensitivity of DDI alerts may compromise patient safety. Thus balancing user needs and patient demands is always a conflicting situation: increasing sensitivity results in increase of inappropriate alerts and decreasing specificity (43) (51). Having studies comparing CDSSs with respect to drug safety alerting could identify best choice CDSS software vendors with highest sensitivity and specificity rates. However such studies are scarce and limited to single-country and usually single-center surveys (9) (10) (43) (44). A factor that contributes to a better “advanced” CDSS performance appears integration of laboratory and clinical patient data. CDSS installed and functioning as part of internal hospital systems appears to be superior compared to isolated CDSS firing DDI alerts by default (9) (10) (43). A “smart” CDSS’s algorithm should generally rely on literature-based evidence and practice-based experience, which means it should always take the clinical scenario into account before reporting DDI alerts: e.g. most frequent DDI alert of risk of hyperkalemia related to treatment of hypokalemia by potassium sparing diuretics and potassium supplement would be suppressed in such system (52). Implementation of such concepts appear a promising strategy in improving specificity of computer-triggered DDI alerts. The knowledge database of a CDSS should be continuously updated by evaluating what effects medication alerts have in daily practice (10).

No significant improvement or benefits to clinical patient outcomes have been demonstrated by this study. On the contrary, current literature review has shown that vast majority of CDSSs used in clinical practice lack these properties altogether.

Limitations
Technical: possibility of exclusion of relevant papers due to the search terms (terminology used to describe CDSS and prescription alerts differs among systems, countries and journals, as later turned out in the search process). This limitation was partially corrected by manual searching for relevant publications;
Publication bias and selective reporting of study findings cannot be excluded;
The studies of interest were heterogeneous in interventions, populations, and outcome measures;
Small sample size of eligible studies;
Many studies were not randomized; DDI alerts appear to lack correlation among different vendors: e.g. a combination of sulpiride and haloperidol is rated as “high danger” by one CDSS provider and only “low risk” by the other (44), alert design was not uniform among studies.

Clinical implications, practical and research recommendations
1. Improvement in CDSS functionality to balance DDI alert appropriateness is highly desirable.
2. Sensitivity and/or PPV of DDI alerts should be systematically reported in CDSS research.
3. Studies assessing effects of CDSS on patient outcomes are needed.

Conclusions
Current CDSSs neither meet the prescribers’ needs, nor are completely acceptable for globalized implementation. The evidence on patient outcome is lacking, and further studies are needed to establish their role in clinical care.
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