

A Systematic Review of Medication Safety and Clinical Outcomes Related to Drug Interaction Software

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1.0 ABSTRACT

Background

Adverse drug events (ADEs) represent an important problem for hospital and primary care. Software that detects potentially adverse drug interactions has been widely implemented in an effort to reduce the rate of ADEs. However, the impact of drug interaction detection software (DIS) on patient safety outcomes remains unknown.

Objective

To systematically review the effectiveness, safety and cost-effectiveness of DIS on patient-relevant outcomes.

Data Sources

We conducted a systematic search of several databases: MEDLINE, EMBASE, IPA, HealthStar and CINAHL.

Study Selection

We included English language, post-1990, prospective studies that examined clinical decision support software that included drug interaction checking and examined adverse drug interactions as an outcome.

Data Extraction

A team of 2 reviewers independently abstracted data on methods, setting, software, patient characteristics, and outcomes. Differences were resolved by consensus, or third expert.

Data Synthesis

Of 5848 citations, only four studies met our inclusion criteria. Many of the excluded studies were not prospective or measured only prescriber attitudes, implementation success or changes in workflow. No study examined the impact of drug interaction software specifically. The 4 included studies were examining decision support software which contained drug interaction checking as a component. They each addressed the rates of drug interaction events but were unable to measure a specific effect of the drug interaction checking component of the intervention. A meta-analysis of these studies showed no significant difference in event rate between intervention and control groups (risk ratio = 0.715, 95% CI 0.40,1.29, p = 0.264).

Conclusion

There are no good quality studies addressing the specific benefits and harms of drug interaction software on medication safety or clinical outcomes. The evidence at present does not support a benefit for these systems or support any policy to widely disseminate their use.

2.0 BACKGROUND

With drug treatment regimens increasing in complexity, there have been numerous studies examining the frequency of adverse events (AEs) and interventions to prevent them. A recent study by Forster et al concluded that 72% of all AEs that occur after discharge from hospital were caused by medications.¹ Health Canada has mandated that the development and implementation of an effective, interoperable Electronic Health Record solution in Canada be an immediate priority in order to aid clinicians.² In response, technology has been rapidly developing to address the needs of clinicians. Computerized decision support systems (CDSS), which provide clinicians with intelligent electronic feedback and advice on individual patients, were designed to improve patient safety and increase the efficiency of care. Many of these were designed to improve medication safety; for example, drug-drug interaction checking, allergy alert and verification, dosage, therapeutic drug monitoring and advice about drug of choice. In previous studies with primary care physicians, we found that drug interactions were routinely in the top 3 topics mentioned as important information needs amenable to electronic solutions.³

However, the current prevailing belief that electronic tools in health care will improve patient safety and cost-effectiveness of care remains unproven. A systematic review conducted by Kaushal et al evaluated CDSS, computer physician order entry (CPOE), and combinations of CDSS and CPOE, and concluded that although medication error rates decreased, the impact on adverse drug events (ADEs) was inconclusive.⁴ Recent reviews by Garg et al⁵ and Kawamoto et al⁶ both evaluated the effect of CDSS and concluded that while practitioner performance in prescribing may have changed, there was no conclusive evidence of improved patient outcomes.

With Health Canada and Canada Health Infoway encouraging the computerization and electronic integration of health care on a national level, there are several essential issues to be resolved urgently. The first is whether CDSS are beneficial to patient outcomes. The second is whether the systems are cost-effective. The costs of health care system-wide computerization with CDSS, are enormous – many billions of dollars. It is irresponsible in a publicly funded system to spend such sums of money without reasonable assurance that the investment is worthwhile. Third, an increasing appreciation for the unexpected harms of CDSS, has highlighted the need to actually measure harm in each study.

The quality surrounding drug interaction reporting is dubious – it is primarily based on individual case reports without denominators to estimate frequency. While previous systematic reviews of drug interactions have developed a method of assessing the quality and clinical severity of drug interaction reports, they demonstrated the lack of rigorous studies of drug interactions and their effect on patient outcomes.^{7,9}

In summary, drug interactions are an excellent topic within the CDSS-patient safety paradigm as systems checking for drug interactions are ubiquitous in electronic health care and they address a perceived information gap of clinicians. However, they are expensive, they are based on poor quality evidence and through potentially erroneous recommendations, they have the potential to lead to harm.⁷⁻¹⁰

3.0 OBJECTIVE

Our objective was to summarize the high quality evidence on CDSS that specifically check for drug-drug interactions, and examines their impact on patient medication safety outcomes and cost-effectiveness. The primary outcome of interest was the avoidance of adverse drug events. Other outcomes of interest were clinical patient outcomes as well as potential harms and costs of the intervention. If sufficient information was provided on outcomes and costs, a cost-effectiveness analysis was planned.

4.0 METHODS

This systematic review followed the protocol set out by the Cochrane Collaboration Handbook of Systematic Reviews.¹¹ We included English-language randomized and non-randomized studies that implemented clinical software either specifically for drug interaction checking or for more general decision support but clearly included drug interaction checking. Outcomes had to be measurable with versus without the software. We included studies that examined software that detected drug-drug, drug-lab or drug food interactions either at the point of prescribing or point of care. Both hospital-based software and software located in primary care facilities were included. In terms of outcomes, the studies had to report a direct patient outcome such as morbidity or mortality, but we also included studies measuring a recognized surrogate of medication safety such as the number of adverse drug interaction events prevented. This surrogate would presumably be the one most closely related to the effect of checking for drug interactions.

Studies were excluded if they: a) did not list a drug interaction-specific outcome, and b) were published before 1990. Screens for date and language were not implemented until full text retrieval due to concerns over the integrity of the citation database data. A hand-search of articles from relevant reviews was included as well.

Two independent reviewers conducted a literature search of the following relevant databases: Medline, EMBASE, CINAHL, IPA and Healthstar using a developed search strategy (Appendix 1). Equivalent terms to “Computer, Software or Decision Support” were combined using the “AND” operator with mapped equivalents of “Drug Interactions, Drug Errors or Drug Monitoring”. To ensure that we captured articles that were not mapped to a subject heading, a wildcard term for electronic prescrib\$ was also included. Titles were assessed for their relevancy; irrelevant titles were discarded from further study. All results were transferred to Reference Manager 11 for organizational and analytical purposes. Any discrepancies on the relevancy of the results between the reviewers were discussed. If no consensus was reached, an impartial assessor was consulted. Abstracts were then assessed for relevancy using a data abstraction form (see Appendix 2), specifically designed for this study. Again, any discrepancies amongst the reviewers were discussed. Any disagreements were solved by consulting an impartial assessor.

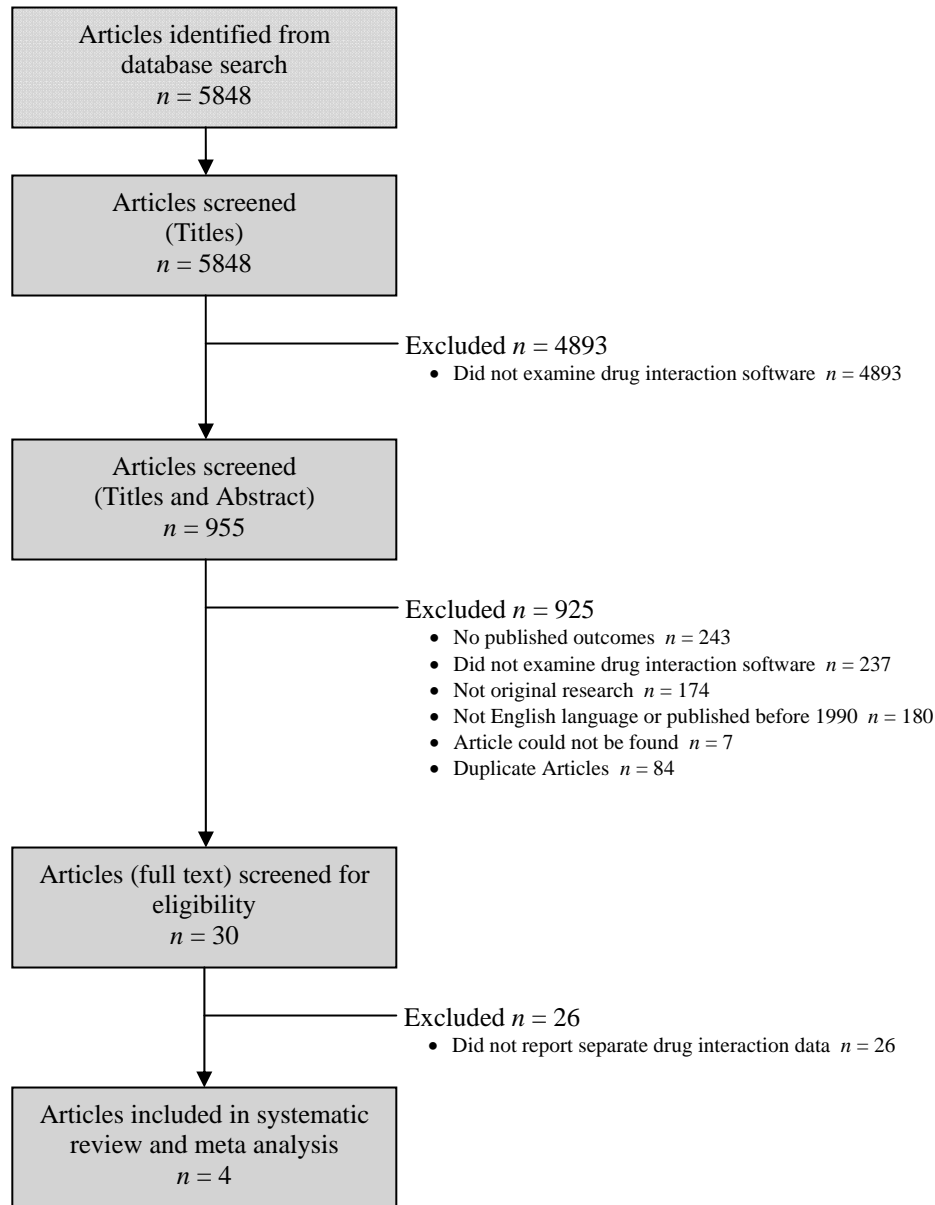
All relevant abstracts were evaluated using a data extraction form which included study design, the quality of the study methods, setting, patient type, details of drug interaction checking software, comparisons, outcomes and cost-benefit variables (see Appendix 3). All results were analyzed using Comprehensive Meta Analysis software

Version 4.2 (<http://www.meta-analysis.com/index.html>) and assessed for potential quantitative meta-analysis.

5.0 RESULTS

In total, the five databases yielded 5848 potential citations for inclusion. Two independent reviewers performed a title evaluation on all of articles, screening for relevance to the research question. Disagreements were discussed and a consensus was attained in each case. None of the articles required the advice of an impartial assessor. The abstracts of the 955 relevant articles were then reviewed. We excluded 925 articles for not meeting inclusion criteria and reviewed the full text of 30 articles. We then excluded 26 articles from the meta-analysis for not distinguishing and publishing DI-specific outcomes. The remaining 4 studies were included in a meta-analysis. Figure 1 outlines this weaning process.

Figure 1. Study Flow Diagram



5.1 DESCRIPTION OF STUDIES

A summary of the four studies selected for data abstraction is presented in Table 1. Three of the studies were conducted in a hospital setting, while one was performed in a primary care environment. The median duration of study was 6 months, (range 5-12 months). Methodological rigor varied between studies and did not clearly improve over time. A total of 80,471 patient days/visits were recorded across all studies. Only one study was a randomized control trial, the others were conducted with a prospective design. Studies are presented in order of methodologic rigour. The study by Tamblyn et al¹³ was a cluster randomized trial in primary care designed to test computerized prescribing support targeted to elderly patients and specific practices considered to be

inappropriate. This included selected drug interaction alerts – those judged to be particularly clinically relevant. The physicians did not use electronic health records but had stand-alone computers and the electronic decision support provided by the study. The baseline rate of inappropriate drug interaction situations was 2.5% and there was no improvement over the course of the study in the intervention group compared to control.

Oliven et al¹⁵ conducted a prospective cohort study examining the effect of CPOE with drug interaction checking as a component, in 2 internal medicine wards. Although the wards were similar on some global demographics, they had a different set of providers as well as the difference in prescribing method – one by CPOE and one by hand. The study was carried out 3 years after the CPOE ward had computerized. The study was able to show a lower rate of drug-drug interactions on the CPOE ward over 6 months, but the rate was low (8% versus 4%) and the poor quality methods render the results susceptible to several biases.

Bates et al¹⁴ used a before-after design with interrupted time series to study the effect of CPOE implementation on medication errors of various types over time. Adverse drug interactions were extremely infrequent at both baseline and study end, with no significant change.

The study by Potts et al¹² used a before-after design to study medication errors before and after a hospital-wide CPOE installation, in a critically ill pediatric population. Their definition of medication errors was extremely broad and included hospital rule violations regarding acceptable abbreviations. There was only 1 drug-drug interaction per 6803 patients in the baseline period and none in the follow-up period in 7025 patients. This difference was not statistically significant.

Table 1. Summary of Included Studies¹²⁻¹⁵

Publication Year	Author	Methods	Patient Population	Total Population	Intervention	Outcome Unit	Control Measure	Original Outcome	Location
2003	Tamblin	Cluster RCT	Primary Care	64753 Patient Visits	CPOE	Inappropriate prescriptions started per 1000 visits causing DI	no CPOE	Inappropriate prescribing	Canada
2005	Oliven	Prospective Cohort	Internal medicine ward	10002 Patient Days	CPOE	Mean DI errors per patient	Handwritten prescriptions	Incidence of prescription errors	Israel
1999	Bates	Prospective Before-After	Two general medicine wards, 1 ICU	3582 Patient Days	CPOE	Number of new DI errors	Baseline	Medication errors	USA
2004	Potts	Prospective Before-After	Pediatric Critical Care Unit	2134 Patient Days	CPOE	New DI Error	Pre-CPOE	Medication Errors	USA

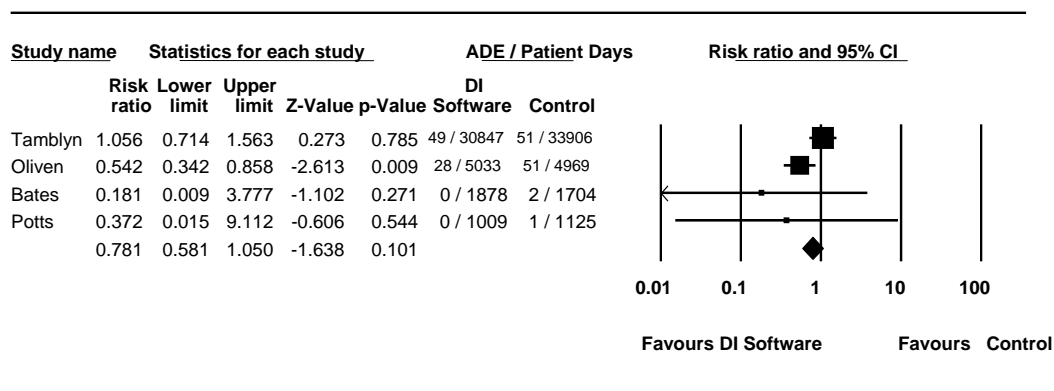
CPOE; computer physician order entry, DI; drug interaction, RCT; Randomized control led trial,

5.2 DATA ABSTRACTION AND META-ANALYSIS

Outcome data were collected for all four studies by comparing the number of recorded adverse drug interaction events per 1000 patient days (the DI events rate) in the control group to the DI events rate in the intervention group. If the DI event rate was not published, the reviewers performed a manual calculation based on the data provided. For the purposes of the analysis, a patient visit in a primary care setting was assumed to be equivalent to a patient day in a hospital. For the cluster RCT, the study's rate ratio with confidence limits was used in the meta-analysis instead of raw event rates, as the former was adjusted for the cluster design. None of the studies provided any data

regarding clinical patient outcomes or economic analyses of the intervention. As a result, no other outcomes could be assessed in the meta-analysis. Figure 2 shows the results of the meta-analysis.

Figure 2. Meta-analysis of Drug Interaction Events



Q-Value	df (Q)	P-Value	I-Squared
5.802	3	0.122	48.297

The pooled analysis showed a non-significant overall effect (risk ratio of 0.72, 95% CI 0.40, 1.29, $p = 0.26$). A random effects analysis was used since statistical tests suggested that the studies were slightly heterogeneous; the Chi-square result was larger than the degrees of freedom.

6.0 DISCUSSION

The limited number of studies that fulfilled the inclusion criteria demonstrates the lack of definitive evidence surrounding drug interaction software. Of 5848 citations, only 4 were deemed clinically relevant for inclusion in a meta-analysis. Many of the potential studies had no patient outcomes reported, nor robust study methods. Even amongst these four studies, none investigated the specific effect of electronic drug interaction checking. Our analysis identified no significant difference caused by the implementation of these software which included drug interaction checking. While it is possible that the drug interaction component of the intervention could have had a separate positive or negative effect on another outcome, this was impossible to measure. None of the studies included or was amenable to an economic analysis. Although several studies mentioned cost or financial benefit, none were explicit enough to critique the claim. The quality of the non-randomized studies was poor - in addition to the lack of randomization which although difficult to implement for a complex intervention, is key to validity, studies used non-blinded, non-uniform assessment of outcomes and in some cases, evaluation by the implementation team. Although the ascertainment of adverse drug interactions, since it was not implemented systematically, could have been suboptimal, the rate of adverse drug interactions was very low. This further throws into question whether a general screening for drug interactions, knowing that the quality of the underlying data on drug interactions is poor, is a worthwhile endeavor. Recognizing that

any electronic intervention because of its complexity, can readily produce more harm than good because of errors, our results suggest drug interaction screening currently cannot be recommended. It makes more clinical sense to concentrate on very high morbidity, well established drug interactions, such as warfarin with certain antibiotics, lithium with certain diuretics, strong CYP3A4 drugs with other narrow therapeutic index drugs, etc.

This systematic review has a few potential limitations. First, we deliberately narrowed the scope of the study to software advising on drug interactions. We cannot comment based on these data, on the impact of CDSS in general. The effect of CDSS has been studied in other systematic reviews, including an attempt to identify which features predict success of the CDSS^{5,16}. Second, excluding non-English studies and abstracts from clinical meetings may have removed results relevant to the study but this is unlikely to have significantly influenced results. Third, we did not contact leading authors for unpublished results. Lastly, we did not test for publication bias, since the overall effect of these studies was negative. However, it is possible that studies in which the effect of drug interaction checking software was harmful, could have been suppressed and remained unpublished. .

The aim of this study was to provide evidence to support or rebut the current policies involving CDSS. With institutions and governments providing large amounts of funding to advance e-health, a rational approach to the assessment of these interventions is warranted. For drug interaction software specifically, many pharmacies invest heavily in the purchase and continual updates to drug interaction software applications to aid in their decision making. However, drug interaction evidence is based on poor quality evidence (mostly case reports and small case series), software to address drug interactions intelligently (adjusted for likelihood and potential clinical impact) is very complicated to develop, and software requires multiple iterations to ensure accuracy and appropriate interpretation. At present, we find no evidence that clinicians and policy makers should invest in general drug interaction screening. Further research should address the effect of screening for selected, high morbidity drug interactions.

7.0 CONCLUSION

There is a significant lack of evidence to support the touted benefits of drug interaction software. Without sufficient evidence, we believe that large investment in wide implementation of these software in clinical practice is premature, and could potentially be harmful. Further research is required to fully explore the potential benefits and harms this type of software has on patient outcomes. We suggest that the software focus on known drug-drug interactions with high resultant morbidity, rather than all potential interactions.

The authors would like to thank Ms. Anita DiLoreto for her contribution and support.

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Appendix 1: Database Search Strategy

HealthStar

Computers OR software OR decision making, computer assisted OR therapy, computer assisted OR e-presc\$ OR electronic presc\$ OR decision support systems, clinical OR decision support techniques AND (drug-interactions OR drug monitoring OR Medication Error)

Medline

Computers OR software OR decision making, computer assisted OR therapy, computer assisted OR e-presc\$ OR electronic presc\$ OR decision support systems, clinical OR decision support techniques AND (drug-interactions OR drug monitoring OR Medication Error)

EMBASE

computer OR computer program OR computer system OR decision making OR computer analysis OR E-pres\$ OR electronic presc\$ OR decision support systems, clinical OR decision support techniques AND (drug interaction OR chemical interaction OR drug monitoring OR Medication error)

CINAHL

decision making, computer assisted OR computers & computerization OR software OR E-pres\$ OR electronic presc\$ OR decision support systems, clinical OR decision support techniques AND (drug interactions OR drug-food interactions OR drug monitoring OR Medication Errors)

IPA

Computers OR Prescribing OR Decision Making OR e-presc\$ OR electronic presc\$ AND Drug Interactions OR monitoring

Appendix 2: Data Relevance Form (Abstract Evaluation)

Data Relevance Form: Evaluation of Drug Interaction Software

Reference ID#:

Primary Author:

Date:

Reviewer:

SW

KW

1. Definitions:

A) Drug-drug interaction: The action of a drug that may affect the activity, metabolism, or toxicity of another drug.

B) Drug-food interaction: The action of consumed nutrition that may affect the activity, metabolism, or toxicity of a drug.

C) Drug-lab interaction: The action of a drug that may affect the specificity, sensitivity, or accuracy of a diagnostic laboratory procedure.

D) Food-lab interaction: The action of consumed nutrition that may affect the specificity, sensitivity, or accuracy of a diagnostic laboratory procedure.

2. Exclusion Criteria:

- Article is an opinion paper or a systematic review (evaluate references for inclusion)
- Retrospective study
- Does not examine a software application that provides clinical support for A, B, C or D
- Study examining software design, with no measurable outcome
- Study comparing various software programs, with no measurable outcome

3. Study Satisfies Inclusion Criteria:

- Yes (proceed with data collection)
- No (document and exclude from analysis)

Appendix 3: Data Extraction Form (Full Article Evaluation)

Data Extraction Form: Evaluation of Drug Interaction Software

Reference ID#: Primary Author: Date:

Reviewer:

SY

KW

I: Study Description

1. Publication Source:

- a. Medline b. EMBASE
c. CINAHL d. IPA
e. Referenced in another article f. Other

2. Language:

- a. English b. French c. German d. Spanish e. Chinese
f. Japanese g. Other

3. Country of Study:

- a. USA b. Canada c. UK d. Australia e. France
f. Germany g. China h. Japan i. Other

4. Funding Source:

- a. Government b. Industry
c. Academic Organization d. Non-Profit / Charity
e. Professional Organization f. Other
g. Unclear h. Unreported

i. Notes:

5. Applicable Definitions:

- a. Drug-Drug Interactions b. Drug-Food Interactions
c. Drug-Lab Interactions d. Food-Lab Interactions
e. Unclear f. Unreported
g. Other

II: Methods/Validity

6. Study Population:

- a. Physicians b. Pharmacists
c. Patients d. Other
e. Unknown f. Number of Participants

7. Intervention:

- a. Number of Alerts b. Number of Alerts Overridden
c. Number of Clinically Significant Alerts d. Other

8. Duration of Study (months):

a.

9. Level of Randomization:

- a. Cluster / Group b. Individual
c. Unknown d. Other

10. Method of Randomization:

- a. Coin Flip b. Randomization Table
c. Alternating Treatment Allocation d. Unclear

e. Not reported

11. Study Setting:

- a. Primary Care b. Teaching Hospital
c. Community Hospital d. Pharmacy
e. Other

12. Intention to Treat Analysis:

- a. Yes b. No
c. Not applicable

13. Reasons for Withdrawal Given:

- a. Yes b. No

14. Adequate Sample Size Calculation:

- a. Yes b. No

15. Outcome Assessment:

- a. Objective b. Subjective with blinding
c. Subjective without blinding but with pre- d. Subjective without blinding or pre-
specified evaluation criteria specified evaluation criteria
e. Unclear

III: Cost-Benefit Analysis

16. Performed:

- a. Yes b. No

17. Perspective:

- a. Patient b. Physician
c. Pharmacist d. Hospital
e. Pharmacy f. Not Reported
g. Other

18. Value Units:

- a. QALY b. Adjusted monetary value
c. Unadjusted monetary value d. Unclear
e. Other