A SYSTEMATIC REVIEW OF MEDICATION SAFETY OUTCOMES RELATED TO DRUG INTERACTION SOFTWARE

Kevin Wong[1,3], Savio KH Yu[1], Anne Holbrook[1,2,3]

[1]Centre for Evaluation of Medicines, Hamilton, Ontario; [2]Division of Clinical Pharmacology & Therapeutics McMaster University, Hamilton, Ontario; [3]Faculty of Pharmaceutical Sciences University of Toronto, Toronto, Ontario

Corresponding Author: *holbrook@mcmaster.ca*

_____

ABSTRACT

Background
Adverse drug events (ADEs) represent an important problem for hospital and primary care. Software that detects potential 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.

Objectives
To systematically review the literature on DIS in preventing adverse drug events and determine the effectiveness and cost-effectiveness of DIS.

Methods
A literature search of MEDLINE, EMBASE, CINAHL, IPA and Healthstar, using terms "Computer, Software or Decision Support" combined with "Drug Interactions, Drug Errors or Drug Monitoring" sought English language, post-1990 prospective studies that examined drug interaction (drug-drug) software as an intervention and adverse drug interactions as an outcome. Relevant studies were analyzed using a Bayesian meta-analysis approach.

Results
Of 5848 citations, only four studies met our inclusion criteria. Most 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 exclusively, rather as a component of decision support software. A Bayesian meta-analysis of these studies showed no significant difference in event rate between intervention and control groups (relative risk 0.66, 95% CI 0.33 to 1.18). The posterior median I-squared was 52%.

Conclusion
No good quality studies address the specific benefits and harms or cost-effectiveness 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.

Keywords: *Drug interactions, computerized decision support systems, adverse drug event, systematic review*
_____

As drug treatment regimens increase in complexity, so do concerns regarding adverse drug interactions and adverse drug events (ADEs). A recent Canadian study concluded that 72% of all adverse events that occurred in hospitalized patients discharged to primary care were related to medication use.[1] The current prevailing belief that electronic tools in health

care will improve patient safety and cost-effectiveness of care remains unproven. Recent reviews evaluating the effectiveness of electronic prescribing or computer decision support systems (CDSS) focused on prescribing (which often include drug interaction checking), show that while practitioner performance and medication error rates may improve, there is no evidence of improved patient outcomes.[2-5]

Health Canada, the federal department responsible for the regulation and monitoring of health products and devices, has made the development and implementation of an effective, interoperable Electronic Health Record in Canada an immediate priority to aid clinicians, in part, to reduce adverse medication events.[6] However, no guidelines have been issued regarding drug interaction software (DIS). In the United States, the American Medical Informatics Association has created an action plan for electronic prescribing, which includes drug interaction checking as a basic requirement.[7] In the United Kingdom, where most primary care physicians use an electronic health record,[8] the National Health Service has moved towards full electronic prescribing, with aims to include drug interaction detection.[9] In response, CDSS, which provide clinicians with electronic feedback and advice on individual patients, have been rapidly developing in hopes of improving patient safety and the efficiency of care. Many of these systems target medication safety - for example, drug-drug interaction checking, allergy alerts, dose adjustment advice and drug monitoring suggestions. In previous studies with primary care physicians, we have found that drug interactions were routinely amongst the top 3 topics mentioned as important information needs amenable to electronic solutions.[10]

As various agencies across the world encourage the computerization and electronic integration of health care, fundamental issues such as relative benefit versus harm and cost-effectiveness, remain unresolved. Unexpected harms related to errors in algorithms, screen display, patient data input or poor attention to clinical severity issues, have only been recently appreciated. Cost-effectiveness is a major question given the billions of dollars required for each country's investment.[11] Regularly updated CDSS systematic reviews still find no consistent evidence of benefit for patient outcomes.[3] All of these issues apply to electronic drug interaction checking systems.

Our previous systematic reviews have highlighted the low quality of the cumulative drug interaction literature - primarily an assorted number of case reports without denominators to estimate incidence or prevalence.[12,13] Unbiased comparisons such as those in a randomized trial, are virtually non-existent in the drug interaction literature. The underlying poor quality of recommendations made about drug interactions compounded with the additional technical and usability problems raised by software, makes it likely that electronic drug interaction software (DIS) has the potential to do more harm than good.[13-16] Yet, DIS is ubiquitously employed by health care professionals such as pharmacists, physicians and nurses as well as integrated in most advanced electronic medical records and e-prescribing systems in health care institutions. No systematic reviews seem to address these important questions of effectiveness, safety and cost-effectiveness of DIS in clinical care.

OBJECTIVE

Our objective was to summarize the evidence on drug interaction software and its impact on patient medication safety outcomes and cost-effectiveness. The primary outcome of interest was the avoidance of adverse drug events, measured as the rate of adverse drug events. Adverse drug interaction events prevented are potential events prevented by the software alerting the clinician. The presumption is that the clinician takes appropriate action, although this is rarely confirmed. Other outcomes of interest were clinical patient outcomes as well as harms and costs of the intervention. If sufficient information was provided on outcomes and costs, a cost-effectiveness analysis was planned.

METHODS

This systematic review followed a process outlined in the Cochrane Collaboration Handbook of Systematic Reviews.[15] We wished to identify English-language randomized or non-randomized studies that evaluated drug interaction software either as a stand-alone product or as part of a larger clinical decision support system but with outcomes measured specific to the DIS. DIS was defined as software to detect and provide alerts regarding drug-drug interactions at the point of prescribing or dispensing.[17] Both hospital and

community settings were included. Although patient outcomes such as morbidity or mortality are the most important, we hypothesized that studies on DIS would not likely be powered to address clinical outcomes. Therefore, surrogate markers for medication safety such as the number of potential adverse drug interaction events prevented, the adverse drug interaction event rate, or the number of inappropriate medications prescribed, were sought. Studies were excluded if they did not measure one of the relevant outcomes, did not provide data that allowed analysis of drug interaction checking vs. control, or were published before 1990. A hand-search of articles from the retrieved reviews was also included.

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). Databases were searched from January 1966 to June 2006. These and similar 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 prescribing (prescrib$) was also included. Titles were assessed for their relevance. Irrelevant titles were discarded from further review. All results were transferred to Reference Manager v11 (Thomson ISI ResearchSoft, Philadelphia, Pa) for organizational and analytical purposes. Any discrepancies on the relevance of the results between the reviewers were discussed. If no consensus was reached, a third assessor was
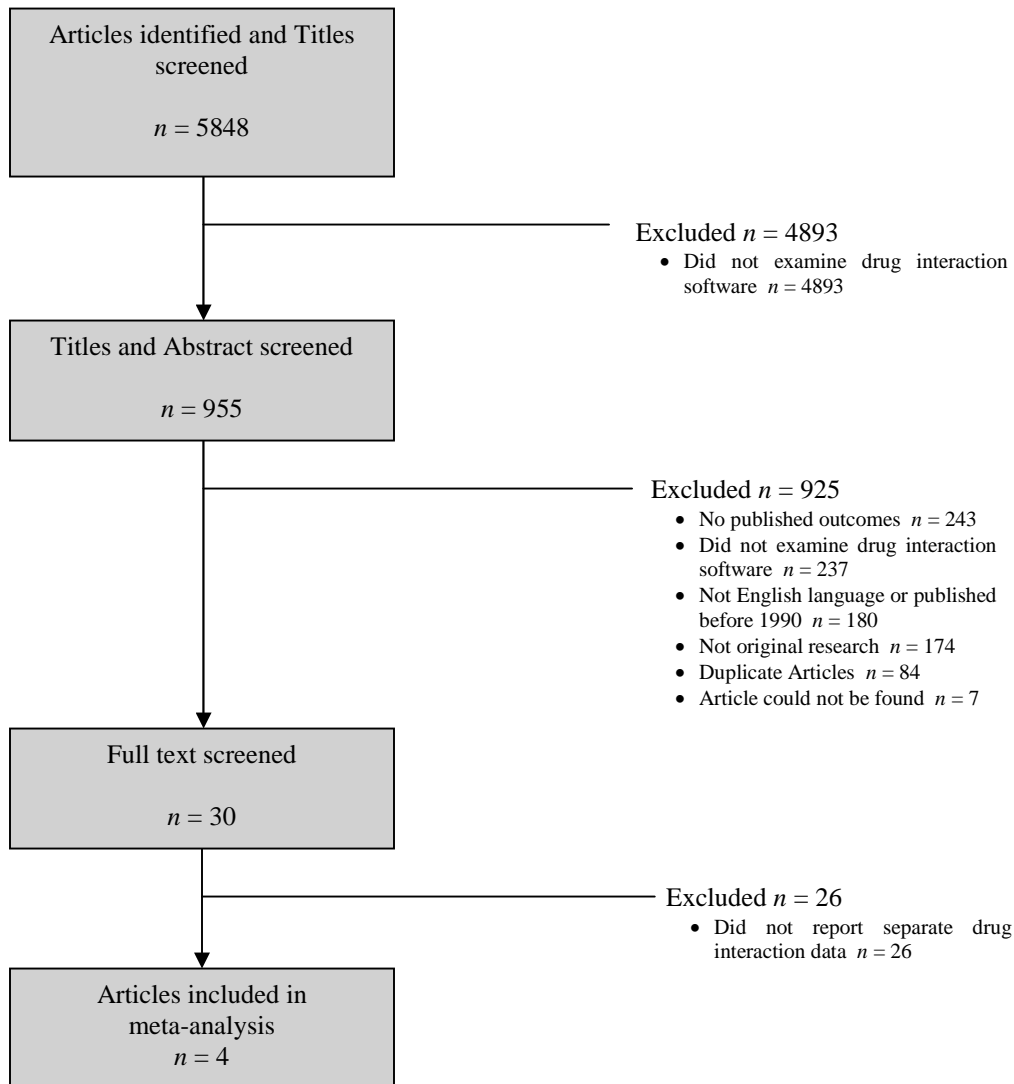
consulted. Abstracts were then assessed for relevance using a data abstraction form (see Appendix 2), specifically designed for this study. Again, any discrepancies amongst the reviewers were discussed with disagreements resolved by the third assessor.

All relevant abstracts then underwent detailed data extraction, which included study design, the quality of the study methods, setting, patient type, details of drug interaction checking software, comparisons, outcomes and economic variables (see Appendix 3). All results were entered in SAS v9.1 (SAS Institute Inc, Cary, NC) and assessed for potential quantitative meta-analysis. A Bayesian meta-analysis random effects model based on a Poisson regression, was conducted to account for the uncertainty in the estimate of between-study variability. Sensitivity analyses were performed to further explore heterogeneity.

RESULTS

The five databases yielded a total of 5848 citations for review. The abstracts of the 955 relevant titles were then reviewed. We excluded 925 of these and reviewed the full text of 30 articles.[3-5,16-42] We then excluded 26 articles from the meta-analysis for not reporting the targeted clinical and surrogate outcomes. For example, excluded studies did not report separate drug interaction data. The remaining 4 studies were included in a meta-analysis.[16,40-42] Figure 1 outlines this weaning process.

FIG. 1   Study Flow Diagram

```
┌─────────────────────────────┐
│  Articles identified and     │
│  Titles screened             │
│                              │
│        n = 5848              │
└─────────────────────────────┘
              │
              │────────────────  Excluded n = 4893
              │                   • Did not examine drug interaction
              │                     software  n = 4893
              ▼
┌─────────────────────────────┐
│  Titles and Abstract screened│
│                              │
│        n = 955               │
└─────────────────────────────┘
              │
              │────────────────  Excluded n = 925
              │                   • No published outcomes  n = 243
              │                   • Did not examine drug interaction
              │                     software  n = 237
              │                   • Not English language or published
              │                     before 1990  n = 180
              │                   • Not original research  n = 174
              │                   • Duplicate Articles  n = 84
              │                   • Article could not be found  n = 7
              ▼
┌─────────────────────────────┐
│  Full text screened          │
│                              │
│        n = 30                │
└─────────────────────────────┘
              │
              │────────────────  Excluded n = 26
              │                   • Did not report separate drug
              │                     interaction data  n = 26
              ▼
┌─────────────────────────────┐
│  Articles included in        │
│  meta-analysis               │
│        n = 4                 │
└─────────────────────────────┘
```

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,[16,40,42] while the fourth was performed in a primary care environment.[41] The median duration of studies was 6 months (range 5-12 months). Methodological rigor varied between studies and did not seem to improve with the more recent studies. A total of 80,471 patient days/visits were recorded across all studies. None of the studies provided any data regarding clinical patient outcomes or cost-effectiveness of the interventions. Only one study was a randomized control trial, the others were conducted with a prospective design.

TABLE 1   Summary of Included Studies[16, 40-42]

Publication Year	Author	Methods	Setting	Total N	Intervention	Outcome Unit	Control Measure	Location
2003	Tamblyn	Cluster RCT	Primary Care	64753 Patient Visits	CPOE	Inappropriate prescriptions started per 1000 visits causing DI	no CPOE	Canada
2005	Oliven	Prospective Cohort	Internal medicine ward	10002 Patient Days	CPOE	Mean DI errors per patient	Handwritten prescriptions	Israel
1999	Bates	Before-After Design (case series)	Two general medicine wards, One ICU	3582 Patient Days	CPOE	Number of DI errors over time	Pre-CPOE	USA
2004	Potts	Before-After (case series)	Pediatric Critical Care Unit	2134 Patient Days	CPOE	New DI Error	Pre-CPOE	USA

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

The study by Tamblyn et al[41] 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-drug interaction alerts – those judged to be particularly clinically relevant. The physicians did not use electronic health records but had stand-alone computers with the electronic decision support provided by the study. The baseline rate of inappropriate drug-drug interaction prescriptions was 2.5% and there was no improvement over the course of the study in the intervention group compared to control.

Oliven et al[42] conducted a prospective cohort study examining the effect of CPOE with drug-drug interaction checking as a component, on 2 internal medicine wards. Although the wards were similar on some global demographics, they had a different set of providers as well as different prescribing methods – one by CPOE and one by hand. The study was carried out 3 years after the CPOE ward had computerized and was able to show a lower rate of adverse drug-drug interactions on the CPOE ward over 6 months (p < 0.01). The remaining two studies employed weaker designs, without concurrent control groups. Bates et al[40] used a before-after design with interrupted time series to study the effect of CPOE implementation on medication errors of various types over 7 months in several medical and intensive care units in a tertiary care hospital. Drug-drug interactions were detected using the DIS. Adverse drug interactions events were rare at both baseline and study end (1.2 /1000 patient days and 0/1000 patient days), with no significant change (p = 0.19). The study by Potts et al[16] used a before-after design to study medication errors before and after a hospital-wide CPOE installation, in a critically ill paediatric population. The DIS was capable of determining drug-drug interactions. 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.

Data Abstraction and Meta-analysis

For all four studies, the number of recorded adverse drug interaction events included a variety of reported results: the absolute number of DIs, the DI rate per patient-days, the DI rate per patient visits, and the DIs ratio per patient. These numbers were standardized using a rate per 1000 patient days as a DI event rate. The DI event rate in the intervention group or intervention period was then compared to the control group or control period. Where the DI event rate was not reported, we were able to calculate it manually. 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. The analysis showed a non-significant overall effect (relative risk is 0.66, 95% CI 0.33 to 1.18). The posterior median I-squared was 52%, indicating insufficient information to assess the impact of study design on between-study heterogeneity. Figure 2 shows the results of the meta-analysis.

FIG. 2   Meta-analysis of Drug Interaction Events
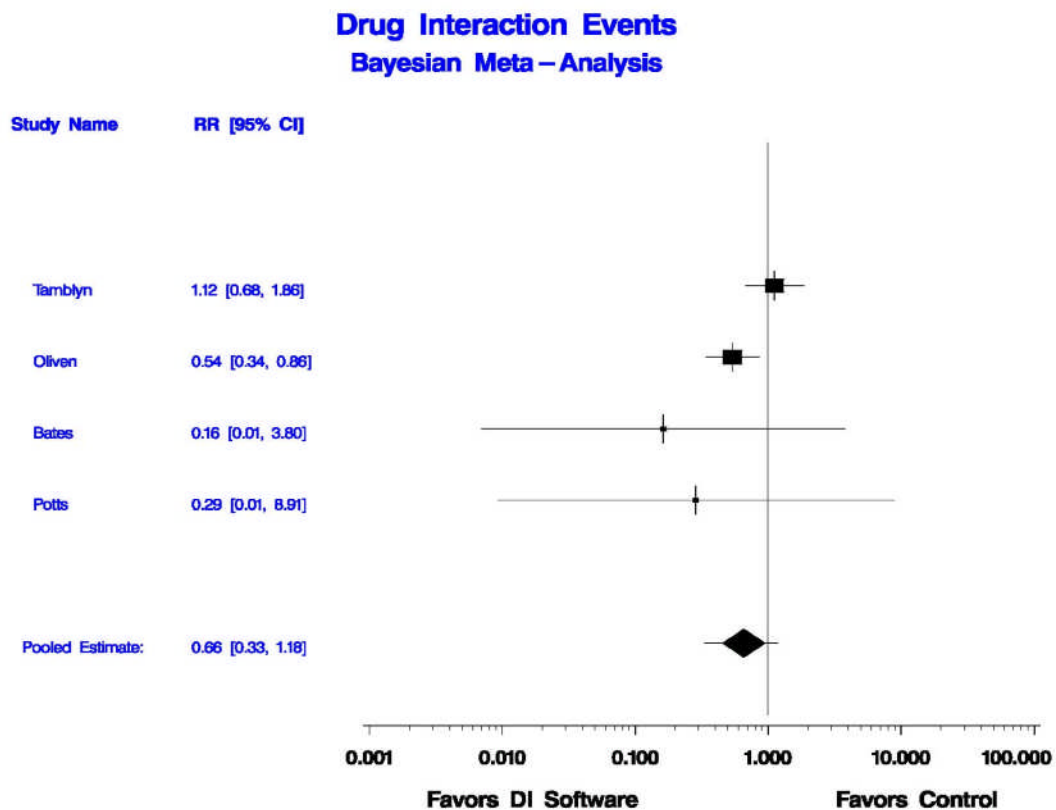
Two sensitivity analyses were conducted, each removing one study from analysis (Tamblyn and Oliven). The Tamblyn paper was excluded first, to see if there was heterogeneity amongst the hospital-based, non-randomized studies. Oliven was excluded in the second analysis as it had a noticeably higher event rate than the other papers. The results of the sensitivity analyses did not assist in reducing heterogeneity. Costs were not elaborated upon in

the included studies, preventing any economic analysis regarding cost-effectiveness.

DISCUSSION

The limited number of studies that fulfilled the inclusion criteria demonstrates the lack of definitive evidence surrounding drug interaction software. Of 5848 potential studies, only 4 satisfied our inclusion criteria of studies measuring even a reasonable surrogate outcome specific to the DIS. Many of the potential studies had no patient outcomes reported, nor an adequate description of study methods. This finding demonstrates the need for further research to identify the direct patient benefit from DIS.

Amongst the four included studies, several problems hampered our analysis. First, none focused on the specific effect of electronic drug interaction checking. Only one study[42] reported a statistically significant effect on adverse drug interactions but the event rate was also unusually high in comparison with the other studies; a potential contributor to the heterogeneity amongst the included studies. Second, none of the included studies was amenable to an economic analysis. Although several studies mentioned cost or financial benefit, none adequately reported outcomes and resource utilization to be able to estimate cost-effectiveness. Third, the non-randomized studies are highly susceptible to bias. In addition to the lack of randomization, which is key to validity, the studies were unblinded, used non-uniform assessments of outcomes, and in some cases, the evaluation of the program occurred after significant resources were used for the implementation. Fourth, as these are complex technology interventions, it is likely that they were imperfectly implemented, including the drug interaction detection component. Finally, the rate of adverse drug interactions in several of the studies was very low, throwing into question whether screening for drug interactions, with its poor underlying information quality, is a worthwhile endeavor at all. No study discussed any prior validation work on the drug interaction knowledge base.

This systematic review has a few potential limitations. First, we deliberately narrowed the scope of the study to software advising on drug interactions, and these results cannot be extrapolated to other forms of CDSS. The effect of CDSS has been studied in other systematic reviews, including an attempt to identify which features predict success of the CDSS.[2] Second, excluding non-English studies, abstracts from clinical meetings and other grey literature may have missed some studies; but, these would not be likely to be high quality studies. 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.

CONCLUSION

There is a distinct lack of evidence to support the touted benefits or cost-effectiveness of drug interaction software. Without sufficient evidence, we believe that large investments to support widespread implementation of these software in clinical practice are premature. The drug interaction literature itself is of insufficient quality to mandate against most drug combinations and the methods of presenting computerized decision support, including drug interactions, require further refinement. Although decreasing medication errors is a laudable goal, health information technology should be held to the commonly accepted and well understood current standards of evidence, which are based on randomized trials examining clinical patient outcomes. We believe that there is an urgent need for higher quality studies exploring drug interactions specifically, then a need for studies exploring the impact of software detecting and alerting clinicians at the point of prescribing of high clinical impact drug interactions.

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 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:

☐ SY   ☐ KW

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

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. ☐   Unclear   c. ☐   Unreported
d. ☐   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

REFERENCES

1. Forster AJ, Clark HD, Menard A, et al. Adverse events among medical patients after discharge from hospital. CMAJ 2004;170(3):345-9.

2. Mollon B, Chong J, Jr., Holbrook AM, Sung M, Thabane L, Foster G. Features predicting the success of computerized decision support for prescribing: a systematic review of randomized controlled trials. BMC Med Inform Decis Mak 2009;9:11.

3. Garg AX, Adhikari NK, McDonald H, et al. Effects of computerized clinical decision support systems on practitioner performance and patient outcomes: a systematic review. JAMA 2005;293(10):1223-38.

4. Kawamoto K, Houlihan CA, Balas EA, Lobach DF. Improving clinical practice using clinical decision support systems: a systematic review of trials to identify features critical to success. BMJ 2005;330(7494):765.

5. Kaushal R, Shojania KG, Bates DW. Effects of computerized physician order entry and clinical decision support systems on medication safety: a systematic review. Arch Intern Med 2003;163(12):1409-16.

6. Health Canada. Electronic Health Record 2003. (2006) http://www.hc-sc.gc.ca/hcs-sss/ehealth-esante/ehr-dse/index_e.html (September 1, 2006).

7. Teich JM, Osheroff JA, Pifer EA, Sittig DF, Jenders RA. Clinical Decision Support in Electronic Prescribing: Recommendations and an Action Plan. (March 1, 2005) http://www.amia.org/inside/initiatives/cds/cdswhitepaperforhhs-final2005-03-08.pdf (September 15, 2006)

8. Schade CP, Sullivan FM, de LS, Madeley J. e-Prescribing, efficiency, quality: lessons from the computerization of UK family practice. J Am Med Inform Assoc 2006;13(5):470-5.

9. National Health Service. Electronic Prescription Service.(2007) http://www.connectingforhealth.nhs.uk/systemsandservices/eps. (September 9, 2008)

10. Holbrook A. COMPETE (2006). http://www.compete-study.com (September 1, 2006)

11. Koppel R, Metlay JP, Cohen A, et al. Role of computerized physician order entry systems in facilitating medication errors. JAMA 2005;293(10):1197-203.

12. Nieuwstraten C, Labiris NR, Holbrook A. Systematic overview of drug interactions with antidepressant medications. Can J Psychiatry 2006;51(5):300-16.

13. Holbrook AM, Pereira JA, Labiris R, et al. Systematic overview of warfarin and its drug and food interactions. Arch Intern Med 2005;165(10):1095-106.

14. Wilson AM, Thabane L, Holbrook A. Application of data mining techniques in pharmacovigilance. Br J Clin Pharmacol 2004;57(2):127-34.

15. The Cochrane Collaboration. Cochrane Handbook Systematic Reviews Interventions 4.2.5. (2005) www.cochrane.org (March 24, 2006).

16. Potts AL, Barr FE, Gregory DF, Wright L, Patel NR. Computerized physician order entry and medication errors in a pediatric critical care unit. Pediatrics 2004;113(1:Pt 1):t-63.

17. Bates DW, Leape LL, Cullen DJ, et al. Effect of computerized physician order entry and a team intervention on prevention of serious medication errors. JAMA 1998;280(15):1311-6.

18. Anonymous. Computerized drug-laboratory interaction alerts change doctors' prescriptions. Res Activities 2006;(305):2.

19. Bates DW. Frequency, consequences and prevention of adverse drug events. J Qual Clin Practice 1999;19(1):13-7.

20. Cavuto NJ, Woosley RL, Sale M. Pharmacies and prevention of potentially fatal drug interactions. JAMA;275(10):1086.

21. Colon L, Armstrong EP, Malone DC, Murphy JE. Evaluation of drug interaction screening software programs in community pharmacies in Tucson, Arizona (Abst). ASHP Midyear Clinical Meeting 39(DEC):P420E.

22. Degnan D, Merryfield D, Hultgren S. Reaching out to clinicians: implementation of a computerized alert system. J Healthcare Qual 2004;26(6):26-30.

23. Dormann H, Muth-Selbach U, Krebs S, Criegee-Rieck M, Geisslinger G. Incidence and costs of adverse drug reactions during hospitalization: computerized monitoring versus stimulated spontaneous reporting. Drug Safety 2000;22(Feb):161-8.

24. Evans RS, Pestotnik SL, Classen DC, Horn SD, Bass SB, Burke JP. Preventing adverse drug events in hospitalized patients. Ann Pharmacotherapy 1994;(4):523-7.

25. George D, Austin-Bishop N. Error rates for computerized order entry by physicians versus nonphysicians. Am J Health Syst Pharm. 2003;60(21):2250-2.

26. Haumschild MJ, Ward ES, Bishop JM, Haumschild MS. Pharmacy-based computer system for monitoring and reporting drug

interactions. Am J Hosp Pharm 1987;44(2):345-8.

27. Hazlet TK, Lee TA, Hansten PD, Horn JR. Performance of community pharmacy drug interaction software. J Am Pharm Assoc 2001;41(2):200-4.

28. Hsieh TC, Kuperman GJ, Jaggi T et al. Characteristics and consequences of drug allergy alert overrides in a computerized physician order entry system. J Am Med Inform Assoc 2004;11(6):482-91.

29. Jankel CA, Speedie SM, McMillan JA. Effectiveness of computerized drug interaction screening programs in hospitals. Drug Information Journal 1990;24(3):513-29.

30. McMullin ST, Reichley RM, Watson LA, Steib SA, Frisse ME, Bailey TC. Impact of a web-based clinical information system on cisapride drug interactions and patient safety. Arch Intern Med 1918; 1999 Sep 27;159(17):2077-82.

31. Mirco A, Campos L, Falcao F, Nunes JS, Aleixo A. Medication errors in an internal medicine department. Evaluation of a computerized prescription system. Pharmacy World & Science 2005;27(4):351-2.

32. Murphy JE, Wang VS, Malone DC, Armstrong EP. Performance of drug interaction software in Tucson hospital pharmacies (Abst). ASHP Midyear Clinical Meeting 39(DEC):P89E.

33. Nebeker JR, Hoffman JM, Weir CR, Bennett CL, Hurdle JF. High rates of adverse drug events in a highly computerized hospital. Arch Intern Med 2005;165(10):1111-6.

34. Papshev D, Peterson AM. Electronic prescribing in ambulatory practice: promises, pitfalls, and potential solutions. Am J Manage Care 2001;7(7):725-36.

35. Rothschild JM, Keohane CA, Cook EF, et al. A controlled trial of smart infusion pumps to improve medication safety in critically ill patients. Crit Care Med 2005;33(3):533-40.

36. Smith DH, Perrin N, Feldstein A, et al. The impact of prescribing safety alerts for elderly persons in an electronic medical record: An interrupted time series evaluation. Arch Intern Med 2006;(10):1098-104.

37. Spencer DC, Leininger A, Daniels R, Granko RP, Coeytaux RR. Effect of a computerized prescriber-order-entry system on reported medication errors. Am J Health Syst Pharm 2005;62(4):416-9.

38. Spina JR, Glassman PA, Belperio P, Cader R, Asch S, Primary Care Investigative Group of the VA Los Angeles Healthcare System. Clinical relevance of automated drug alerts from the perspective of medical providers. Am J Med Qual 2005;20(1):7-14.

39. Steele AW, Eisert S, Witter J, et al. The effect of automated alerts on provider ordering behavior in an outpatient setting. Plos Medicine 2005;(9):864-70.

40. Bates DW, Teich JM, Lee J, et al. The impact of computerized physician order entry on medication error prevention. J Am Med Inform Assoc 1999;6(4):313-21.

41. Tamblyn R, Huang A, Perreault R, et al. The medical office of the 21st century (MOXXI): effectiveness of computerized decision-making support in reducing inappropriate prescribing in primary care. CMAJ 2003;169(6):549-56.

42. Oliven A, Michalake I, Zalman D, Dorman E, Yeshurun D, Odeh M. Prevention of prescription errors by computerized, on-line surveillance of drug order entry. Int J Med Inform 2005;(5):377-86.