Information technology interventions to improve medication safety in primary care: a systematic review

MIRIAM LAINER1,†, EVA MANN1,†, AND ANDREAS SÖNNICHSEN2

1Institute of General Practice, Family Medicine and Preventive Medicine, Paracelsus Medical University, Strubergasse 21, Salzburg 5020, Austria, and 2Institute of General Practice and Family Medicine, University of Witten/Herdecke, Germany

Address reprint requests to: Miriam Lainer, Institute of General Practice, Family Medicine and Preventive Medicine, Paracelsus Medical University, Strubergasse 21, Salzburg 5020, Austria. Fax: +43-662-442002-1209; E-mail: miriam.lainer@pmu.ac.at

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Abstract

Purpose. Improving medication safety has become a major topic in all clinical settings. Information technology (IT) can play an important role to prevent adverse drug events (ADEs), but data on the effectiveness of IT interventions are controversial. The objective of this paper is to provide a systematic review about the effects of IT interventions on medication safety in primary care.


Study selection. Randomized controlled trials (RCTs), if interventions based on IT, performed in primary care and outcomes reported on medication safety.

Data extraction. Study characteristics and outcome data independently extracted by two reviewers. Disagreement resolved by discussion with a third reviewer.

Results of data synthesis. Out of 3918 studies retrieved, 10 RCTs met the inclusion criteria. Of the six studies evaluating computerized provider order entry (CPOE) with clinical decision support (CDS) only 3 studies effectively reduced unsafe prescribing. Both pharmacist-led IT interventions decreased the prescription of potentially inappropriate medication or unsafe prescribing in pregnancy. No reduction of ADEs was achieved by a web program or a TeleWatch system intervention.

Conclusion. Only 5 of 10 RCTs revealed a reduction of medication errors. CPOE with CDS was effective if targeted at a limited number of potentially inappropriate medications. The positive results of pharmacist-led IT interventions indicate that IT interventions with inter-professional communication appear to be effective. The unequivocal results of the included RCTs stress the necessity of rigorous evaluation prior to large-scale implementation.

Keywords: systematic review, information technology, medication safety, adverse drug events, primary care, clinical decision support

Introduction

Various interventions using information technology (IT) have been developed to improve medication safety, and IT has become a main priority since ‘To Err is Human’ has been published in 1999 [1]. Medication errors are recognized as the single most preventable cause of patient harm, and their reduction is of increasing importance, particularly in primary care [2, 3]. A review identifying the frequency and nature of medical errors in primary care found that prescribing errors occur in up to 11% of all prescriptions, mainly related to dosing errors [2]. Recently, a systematic review on the prevalence of adverse drug events (ADEs) found that the median preventable ADE rates were 16.5% in ambulatory-care-based studies and 52.9% in hospital-based studies, respectively [4]. Theoretically, the use of computer systems to identify patients, who are at risk for medication errors, is a powerful method for ‘error trapping’ that may allow physicians to correct errors before patients are harmed. IT-based interventions including computerized provider order entry (CPOE) with clinical decision support (CDS), telemedicine interventions or other IT interventions have been widely promoted as the most promising approaches for improving medication safety across all clinical settings [5]. Previous reviews on the impact of IT interventions on safety of medical care

†These authors contributed equally to this work.
mainly focused on hospital settings. They found benefits in therapeutic control, reduction of toxic drug levels and length of hospital stay [6, 7]. One systematic review published in 2007 assessed the effect of CPOE on safety among various other outcomes in the outpatient setting [8]. However, this review has some limitations with regard to our research question. It excluded other IT interventions than CPOE, was not focused solely on primary care, and only 4 out of the 30 studies included assessed the effect of CPOE on adverse drug events, which was found to be non-significant.

In summary, the existing evidence about the effectiveness of IT interventions to improve medication safety in primary care and also about potential harms of these interventions is scarce. We therefore aimed at the assessment of the effectiveness of any IT intervention in the improvement of medication safety in primary care.

Methods

Research question

Our research objective was to investigate whether IT interventions improve medication safety compared with usual care without IT intervention. Improvement of medication safety was defined as a reduction of medication errors, adverse drug events and adverse drug reactions in patients receiving medication in primary care, which was defined as the primary point of care, involving all outpatient settings including nursing homes and emergency departments. The PICOS format of our research question is depicted in Table 1.

Eligibility criteria

We included randomized controlled studies if they investigated IT interventions, were performed in the primary care setting and reported on at least one of the following outcomes: adverse drug events, prescribing and monitoring errors, dosing errors, potentially inappropriate medications, therapeutic duplications, hospitalization or other outcomes associated with medication safety. Descriptive studies without comparison group, cohort studies, case–control studies, narrative reviews, case reports, commentaries and study protocols were excluded.

Search strategy


Our search strategy combined search terms around IT systems, adverse drug events and primary or ambulatory care. Table 2 shows the terms used in our search. Articles from all languages were included. The inclusion criteria are described below. Furthermore, a manual search was performed using the references of all eligible studies retrieved in the electronic search.

Definitions

Medication error. For definition of medication errors we used the National Coordinating Council for Medication Error Reporting and Prevention definition of medication errors: “any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient or consumer. Such events may be related to professional practice, health care products, procedures and systems, including prescribing, order communication, product labelling, packaging, nomenclature, compounding, dispensing, distribution, administration, education, monitoring and use” [9].

Adverse drug event. ADE is determined according to the definition of Bates et al. [10]: ‘An injury resulting from medical intervention related to a drug’.

Adverse drug reaction. ADR is defined as a ‘response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis or therapy of disease or for the modification of physiologic function’ [11].

As demonstrated in Fig. 1, ADEs may or may not result from medication errors. If they are not medication errors they are considered ADRs.

Data extraction and analysis

Two reviewers independently screened titles and abstracts of studies identified in the electronic search for possible inclusion. The full text of all possibly eligible studies was then assessed by the same two reviewers independently for final inclusion. Discrepancies between the two reviewers were resolved by consensus. A third reviewer was involved if consensus could not be reached.

Following a previously defined data extraction scheme, characteristics of included studies were extracted regarding type of intervention, participants and outcome parameters. For reasons of comparability we recorded or—if not provided—calculated the RR (relative risk) or OR (odds ratio) of all comparisons between intervention and control if possible.

| P: patients | Patients receiving medication in the primary care setting (any primary point of care, defined as any outpatient setting including nursing homes and emergency departments) |
| E: intervention | Any IT intervention such as CPOE, CDS, PIMS or any other computer system addressing medication safety |
| C: comparison | Usual care |
| O: outcome | Improvement of medication safety, defined as a reduction of medication errors, ADEs and adverse drug reactions |
| S: study type | Randomized controlled trials |

IT, information technology; CPOE, computerized provider order entry; CDS, clinical decision support; PIMS, pharmacy information management system.
Assessment of risk of bias in included studies

For the assessment of risk of bias in the included randomized controlled trials we used the Cochrane Collaboration’s assessment tool, which recommends addressing six specific domains to be described in a ‘risk of bias’ table. These domains are sequence generation and allocation concealment to avoid selection bias, blinding of participants, personnel and assessors to prevent performance bias, incomplete outcome data to avoid attrition and detection bias and selective outcome reporting to prevent reporting bias. Disagreement between the two reviewers was resolved by discussion, and if necessary by arbitration involving a third reviewer.

Results

Our electronic and manual search retrieved a total of 3918 articles of which full-text was ordered for 66 studies. Full text assessment of these studies led to the exclusion of 56 studies. The reasons for exclusion are depicted in the flow diagram (Fig. 2). Finally, 10 randomized controlled trials met the inclusion criteria for study design and outcome, and were included in the review.

Study design and setting

Studies were categorized according to the type of IT intervention into three groups: CPOE with CDS, pharmacist led and telemedicine studies.

Six studies reported on CPOE with CDS system [12–17], two studies assessed pharmacist-led IT interventions [18, 19] and two RCTs evaluated a web program and a TeleWatch system intervention [20, 21]. Three studies had a cluster-randomized design. They included 107 and 28 primary care physicians [14, 15], respectively, and 29 resident care units [13]. The 7 remaining studies comprised 42 [16] and 63 emergency physicians [17], 49 [21] and 333 patients [20], 59 680 health plan members [19], 68 residents [12] and 11 100 pregnant women [18]. Considerable heterogeneity in baseline characteristics, outcome measures and statistical analysis prohibited the conduction of a meta-analysis.

Definition of IT interventions

**CPOE and CDS system.** CPOE is the process of entering medication orders or other physician instructions electronically rather than on paper charts. CDS systems are active knowledge systems, which use two or more items of patient data to generate case-specific advice [22–24]. CDS systems match characteristics of an individual patient to a computerized knowledge base, with software algorithms applied to generate patient-specific recommendations, such as dosage and alternative medication suggestions.
duplicate therapy warnings and drug–drug and drug–allergy interaction checking.

Pharmacy information management systems. Pharmacy information management systems (PIMS) are computer systems that have been designed to automate the provision and management of pharmacies' services. They facilitate reporting, active monitoring and retrieval of information to provide interaction checking, allergy screening and contraindication alerts or other possible medication-related complications [25].

Telemedicine. Telemedicine is defined as the use of medical information exchanged from one site to another via electronic communications to improve patients' health status. Telemedicine encompasses different services regarding consultation, diagnosis and treatment.

Results of the reviewed literature

The study results are organized according to the type of intervention (CPOE with CDS, pharmacist-led and telemedicine interventions), outcomes (prescribing errors, adverse drug events) and significance of results (significant, non-significant).

CPOE with CDS

Prescribing errors. Five studies assessed prescribing errors as the main outcome. In the study by Berner et al. [12], intervention clinicians prescribed more safely than controls after receiving CDS, which was a risk rule integrated in a hand-held PDA-based CDS system that provided recommendations for risk assessment and treatment with NSAID only for patients with increased gastrointestinal risk (ANCOVA effect size 0.54, \( P < 0.05 \)). The first study published by Tamblyn et al. in 2003 analysed CDS providing alerts when detecting a limited number of interactions judged clinically important by a consensus panel. This CDS reduced the number of new potentially inappropriate prescriptions [RR (Poisson regression) = 0.82 (95% CI 0.69–0.98)] but did not provoke discontinuation of on-going inappropriate prescriptions [RR (Poisson regression) = 1.06 (95% CI 0.89–1.26)].

In the first study by Terrell et al. [16] a CDS effectively decreased excessive dosing of targeted medications in older patients with renal insufficiency [OR (mixed effects) 4.3 (95% CI 1.3–8.2); \( P = 0.001 \)]. In their second study, a CDS advising against the use of nine potentially inappropriate medications for seniors and recommending safer substitute therapies was successful in reducing visits with an inappropriate medication prescription [OR (mixed effects) 0.55 (95% CI 0.34–0.89), \( P = 0.02 \) and the overall proportion of potentially inappropriate medications [OR (mixed effects) 0.59 (95% CI 0.41–0.85), \( P = 0.006 \)] [17].

In a second study published by Tamblyn et al. in 2008 automated versus on-demand CDS was not effective in reducing
<table>
<thead>
<tr>
<th>Source / design</th>
<th>Study duration</th>
<th>Participants/unit of randomization (R)</th>
<th>Intervention/ control</th>
<th>Outcome</th>
<th>Results</th>
<th>RR, OR, effect size (95% CI)</th>
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<tr>
<td>Berner ES [12], 2006, UK</td>
<td>Not stated</td>
<td>68 residents (R)/189 patient encounters</td>
<td>CDS with NSAID-risk rule/ CDS</td>
<td>Safe prescribing of NSAIDs</td>
<td>A mean proportion of cases per physician with unsafe prescription (ANCOVA): intervention: 23%, control: 45%</td>
<td>ANCOVA effect size 0.54, P &lt; 0.05</td>
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<tr>
<td>Tamblyn R [14], 2003, Canada/ Cluster</td>
<td>13 months</td>
<td>107 primary care physicians (R)/12,560 elderly patients &gt; 65 years</td>
<td>CDS/usual care</td>
<td>(I) New potentially inappropriate prescriptions (II) Discontinued pre-existing inappropriate prescriptions</td>
<td>(I) Number of new potentially inappropriate prescriptions per 1000 visits: intervention: 43.8, control: 52.2 (II) Number of discontinued pre-existing inappropriate prescriptions per 1000 visits: intervention: 71.4, control: 67.4</td>
<td>(I) RR (Poisson regression): 0.82 (0.62–0.98) (II) RR (Poisson regression): 1.06 (0.89–1.26)</td>
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<td>Tamblyn R [15], 2008, Canada/ Cluster</td>
<td>6 months</td>
<td>28 primary care physicians (R)/3449 patients</td>
<td>CDS automated/ on demand</td>
<td>Prescribing problems</td>
<td>Proportion of patients with one or more prescribing problems at the end of the intervention period: computer-triggered: 38.8%, on-demand: 30.1%, P = 0.17</td>
<td>OR: 1.31 (0.89–1.92)</td>
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<tr>
<td>Terrell KM [16], 2009, US</td>
<td>30 months</td>
<td>63 emergency physicians (R)/5162 older patients</td>
<td>CPOE with CDS/ CPOE</td>
<td>(I) Inappropriate prescriptions (II) Visits with at least one inappropriate prescription</td>
<td>(I) Proportion of inappropriate prescriptions: intervention: 5.4%, control: 3.4%, P = 0.006 (II) Proportion of visits with at least one inappropriate prescription: Intervention: 2.6%, control: 3.9%, P = 0.02</td>
<td>(I) OR (mixed effects): 0.59 (0.41–0.85) (II) OR (mixed effects): 0.55 (0.34–0.89)</td>
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<td>Terrell KM [17], 2009, US</td>
<td>24 months</td>
<td>42 physicians (R)/2783 adult patient with renal insufficiency</td>
<td>CPOE with CDS/ CPOE</td>
<td>Excessively dosed medications</td>
<td>Proportion of targeted medications excessively dosed: intervention: 43%, control: 74% Effect size 0.31 (0.14–0.49), P = 0.001</td>
<td>OR (mixed effects): 4.3 (1.3–8.2)</td>
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<tr>
<td>Gurwitz JH [13], 2008, Canada/ Cluster</td>
<td>12 and 6 months</td>
<td>29 resident care units (R)/1118 residents</td>
<td>CPOE with CDS/ CPOE</td>
<td>ADEs</td>
<td>Rate of ADE per 100 resident months: intervention: 10.8%, control: 10.4%</td>
<td>RR (Poisson regression): 1.06 (0.92–1.23)</td>
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<tr>
<td>Raebel MA [18], 2007, US</td>
<td>3 months</td>
<td>11 100 potentially pregnant women (R)</td>
<td>PIMS drug alert/ usual care</td>
<td>Dispensing of category D or X medication</td>
<td>Proportion of patients dispensed targeted medications (any D or X drugs): intervention: 2.9%, control: 5.5%, P &lt; 0.001</td>
<td>OR: 0.52 (0.43–0.63)</td>
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medication errors \[OR 1.31 (95\% CI 0.89–1.92); P = 0.17\] [15]. In both groups, the majority of alerts were ignored (computer triggered: 75.8\%; on demand: 90\%).

Adverse drug events. In the study conducted by Gurwitz et al. [13], a CDS providing alerts in the form of warning messages to physicians caring for patients in resident care units resulted in no significant reduction of overall ADEs \[RR (Poisson regression) 1.06 (95\% CI 0.92–1.23)\] and preventable ADEs \[RR (Poisson regression) 1.02 (95\% CI 0.81–1.30)\].

Pharmacist-led IT interventions

Prescribing errors. In two trials studying a pharmacist-led IT intervention, Raebel et al. [18] demonstrated the effectiveness of a PIMS plus collaboration between healthcare professionals in decreasing the prescribing of 11 pre-specified potentially inappropriate medications in older patients \[OR 0.84 (95\% CI 0.75–0.94), P = 0.002\] and high-risk medications in pregnancy \[OR 0.52 (95\% CI 0.43–0.63), P < 0.001\] [19]. However, the latter of these two trials had to be stopped after 4 months of intervention due to false-positive alerts, i.e. a misidentification of medications as contraindicated, and failure of pregnancy recognition caused by a delay in data transfer.

Telemmedicine interventions

Adverse (drug) events. In the study published by Spaeder et al. [21] remote monitoring with an automated telemedicine system was used to facilitate medication titration in patients with congestive heart failure. In the second study a web program supported patients to early recognize relapse in inflammatory bowel disease and start medication [20]. Although medication safety was not the primary outcome of these two studies and thus the studies may have been underpowered for this outcome, we decided to include them in our review, as adverse (drug) events were important secondary outcomes. Neither of the two interventions reduced adverse (drug) events.

Detailed results of all studies are depicted in Table 3.

Assessment of risk of bias

We included 10 randomized controlled studies in the review [12–21]. Out of the three cluster randomized controlled studies [13–15], only two accounted for the cluster design and calculated intra-cluster-correlation coefficients [14, 15]. The methodological quality of all included studies is presented in Table 4. Only six studies clearly reported adequate sequence generation [12, 16–20]. The remaining studies gave insufficient detail to judge whether there was adequate sequence generation or not.

Four studies reported adequate concealment of allocation [16, 18–20]; six did not [12–15, 17, 21]. In one study concealment of allocation was unclear since the authors described potential for contamination [16]. Only two studies reported blinded assessment of outcomes [13, 17], in all other studies this was not stated or remained unclear.

Only one study reported that outcome data [18] were incomplete, in all the other studies possible incompleteness was
not addressed [12, 20, 21] or remained unclear [13–17, 19]. Three studies provided information about follow-up for the outcomes [12, 20, 21]. In all of these three studies dropout rates between the intervention and the control groups differed by 50% or more [12, 20, 21]. The reporting of the study that was stopped early was judged as selective [18]. A sample size calculation was only performed in the study published by Gurwitz et al. [13]. As a safeguard against publication bias and selective reporting, the International Committee of Medical Journal Editors introduced mandatory registration of all RCTs as a precondition of publication in 2005 [26]. However, none of the studies included in our review had been registered. Therefore, the outcomes reported in the respective methods and results sections of the publications could not be compared with pre-specified outcomes in a trial registration or study protocol, and thus selective reporting or a post hoc change of primary and secondary endpoints cannot be excluded. Overall, all studies included in the review were marked by considerable risk of bias.

**Discussion**

Our systematic review evaluated the benefit of three categories of IT interventions on medication safety in primary care: CPOE with CDS, pharmacist-led IT interventions and telemedicine interventions.

CDS systems were effective only if they targeted a limited set of potentially inappropriate drugs, and/or pre-specified medication problems in risk groups, e.g. patients with renal insufficiency [12, 16, 17]. When decision support systems were based on an overly inclusive database with extensive information about, e.g. potential drug–drug interactions, physicians seemed to be overwhelmed by the complexity of information. To focus on only a limited number of relevant drugs to be avoided seems to be an effective approach.

Interestingly, there was a selectively greater impact of CDS on the initiation of medication rather than on the discontinuation of inappropriate pre-existing medication [14–16]. It appears that patients as well as prescribers are reluctant to stop a drug in situations in which a patient tolerates it well despite published literature of risk with the treatment. For future studies it may be important to recommend discontinuation of pre-existent drug treatment only if the risk is considerable.

Physicians tended to stop the CDS tool or to override alerts if there was poor signal-to-noise ratio, if alerts were judged as irrelevant, or if they were shown repeatedly [27]. Alert fatigue appears to be the most probable explanation why automated alerts were not superior to on-demand alerts in the study conducted by Tamblyn et al. [15]. This finding has important implications for the design of future interventions. One of the most important challenges will be to improve the effectiveness of CDS by reducing alert burden to only clinically relevant alerts. Decision support systems should provide valid data on safer

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**Table 4** Assessment of risk of bias

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<td>Raebel MA [19], 2007</td>
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<td>Elkjaer M [20], 2010</td>
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<td>Spaeder J [21], 2006</td>
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+ = yes (low risk of bias); ? = unclear (risk of bias unclear); - = no (high risk of bias).
Prescription and should therefore be restricted to evidence-based recommendations, avoiding non-evidence-based alerts and those of minor importance. Yet, comprehensive valid drug databases still need to be developed. Finally, to further facilitate judgement about risk relative to benefit, CDS may also be required to integrate additional clinical data and laboratory information in order to tailor recommendations to the individual patient.

Another important finding of our systematic review was that some errors were related to the insufficient reliability of the IT. These errors not only compromised the validity of the study results. Even more importantly, they raise safety concerns, which must be seen as an important component of e-iatrogenesis [28]. Thus, system errors in one study produced unnecessary alerts and inappropriate treatment recommendations, and therefore the study had to be discontinued [15].

In a second study, the electronic system was only targeted at newly prescribed drugs and thus could not assess the total 24-h dose of a drug that was already in use and relate it to the recommended dose range [13]. Again, this example of system error reflects the potential harm of IT interventions and demands for the development of more robust and reliable technology.

A third study had to be stopped because of misidentification of medications contraindicated in pregnancy and misidentification of pregnancy due to delayed transfer of diagnosis [18]. These findings add to the knowledge that optimization of CDS applications is urgently needed to protect patients from harms resulting from IT interventions.

Both studies assessing pharmacist-led IT interventions were successful in reducing medication errors. These results suggest that detection of unsafe medication by pharmacists together with feedback to and discussion with physicians may be an additional safeguard in the complex process of prescribing. This finding is supported by another recently published study, which showed that communication between pharmacists and physicians, education of staff together with patient counselling significantly improved prescribing safety [29].

The two telemedicine studies, which assessed ADEs as a secondary outcome [20, 21] did not reveal any significant reduction of ADEs in comparison with usual care. Although these two studies were underpowered regarding the evaluation of ADEs, they parallel the findings of a recent Cochrane review of RCTs performed in the hospital setting [7].

In summary, IT interventions have been shown to be successful in reducing medication errors. These results suggest that detection of unsafe medication by pharmacists together with feedback to and discussion with physicians may be an additional safeguard in the complex process of prescribing. This finding is supported by another recently published study, which showed that communication between pharmacists and physicians, education of staff together with patient counselling significantly improved prescribing safety [29].

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References


