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SYSTEMATIC REVIEW

Impact of Interventions Designed to Reduce Medication Administration Errors in Hospitals: A Systematic Review

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Abstract

Background There is a need to identify effective interventions to minimize the threat posed by medication administration errors (MAEs).

Objective Our objective was to review and critically appraise interventions designed to reduce MAEs in the hospital setting.

Data sources Ten electronic databases were searched between 1985 and November 2013.

Methods Randomized controlled trials (RCTs) and controlled trials (CTs) reporting rates of MAEs or related adverse drug events between an intervention group and a comparator group were included. Data from each study were independently extracted and assessed for potential risk of bias by two authors. Risk ratios (RRs, with 95 % confidence intervals [CIs]) were used to examine the effect of an intervention.

Key Points

Reduction in rates of medication administration errors (MAEs) and related adverse drug events (ADEs) were reported for some medication use technology (automated dispensing, barcoding, and electronic prescribing) and nurse educational training (simulated learning and pharmacist-led training) interventions.

All included studies were subject to potential bias in study design, and the use of chart review and/or self-reported data for some technological-, ward system-, and anesthesia-based interventions reduced the confidence that could be placed in their findings due to likely underestimation of MAE rates.

Key considerations for the design and testing of future interventions designed to minimize MAEs and related ADEs include the use of theory-driven evidence of their causes to inform design; standardization of research methods and reporting (using direct observation and separation of subgroups); incorporating all MAE types and measuring error severity.

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Results Six RCTs and seven CTs were included. Types of interventions clustered around four main themes: medication use technology ($n = 4$); nurse education and training ($n = 3$); changing practice in anesthesia ($n = 2$); and ward system changes ($n = 4$). Reductions in MAE rates were reported by five studies; these included automated drug dispensing (RR 0.72, 95 % CI 0.53–1.00), computerized physician order entry (RR 0.51, 95 % 0.40–0.66), barcode-assisted medication administration with electronic administration records (RR 0.71, 95 % CI 0.53–0.95), nursing education/training using simulation (RR 0.17, 95 % CI 0.08–0.38), and clinical pharmacist-led training (RR 0.76, 95 % CI 0.67–0.87). Increased or equivocal outcome rates were found for the remaining studies. Weaknesses in the internal or external validity were apparent for most included studies.

Limitations Theses and conference proceedings were excluded and data produced outside commercial publishing were not searched.

Conclusions There is emerging evidence of the impact of specific interventions to reduce MAEs in hospitals, which warrant further investigation using rigorous and standardized study designs. Theory-driven efforts to understand the underlying causes of MAEs may lead to more effective interventions in the future.

1 Background

It is now widely acknowledged that healthcare can inadvertently harm patients, with a median of 9.2 % (4.6–12.4) of hospital admissions suffering at least one adverse event worldwide [1]. Adverse events associated with medication (adverse drug events [ADEs]) are a chief contributor to overall patient harm and commonly involve medication administration [1, 2]. Though estimates vary, a median of over one-third of ADEs have been considered preventable [2] and arise due to medication errors (MEs) [3]. MEs may affect drug administration stages frequently [4], thus making administration an important area for quality and safety improvement [5]. To emphasize this need further, the median rate of medication administration errors (MAEs) in hospitals has been reported as 19.1 % of 'total opportunities for error' [5], with much greater rates for intravenous (IV) MAEs [5, 6].

In order to design effective interventions to minimize MAEs, it is important to understand what causes them [7]. A systematic review of the causes of MAEs found that they arose due to deficiencies in communication between colleagues; medication supply problems; interruptions/distractions; patient-related factors (e.g. acuity); inadequate equipment; and poor physical/mental health of staff, amongst other causes [8]. Evidence suggests that multiple interconnecting causes are responsible for prescribing and administration errors [7–10], and that a combination of MEs from either within or between medication use stages contribute to the development of ADEs [4]. Any forthcoming remedial interventions may therefore need to reflect this level of complexity [4, 7–10].

Interventions suggested to reduce MAEs in hospitals include use of information technology; staff training in calculations and medicines use; proper labeling of medicinal products; improved access to pharmacy services; outsourcing supply of high-risk products; and redesign of medicines storage and preparation areas [11, 12]. Systematic reviews have been carried out that evaluated reductions in MAEs through utilization of barcode technology [13], interventions designed to minimize interruptions [14], and double-checking processes [15]. Other literature reviews have considered MAEs as part of an overall assessment of the effect of preventive measures on MEs. These include a variety of measures with reference to older adults [16], and critical care patients [17], as well as physician order entry with or without decision support [18, 19].

No systematic reviews have examined all types of interventions designed to impact on MAEs in hospitals. Although informative, the review papers above do not assess interventions designed to address a wider range of known MAE causes, and, despite them all assessing or commenting on study quality in some way, the process and criteria varied considerably. Many also included studies without comparator groups, which reduces the certainty with which changes in outcome measure(s) are attributable to the intervention [20], increasing the likelihood of bias in determining which are most appropriate for implementation in practice.

Given the emerging knowledge surrounding the causes of MAEs, a focused systematic review of the published literature is required. This study was undertaken to identify and critically appraise the evidence relating to interventions designed to impact on MAEs in hospitals.

2 Literature Search Method

2.1 Search Strategy

The search strategy was developed by RNK (protocol available from the authors). Ten electronic databases were searched by RNK: EMBASE, MEDLINE, Health Management Information Consortium, International Pharmaceutical Abstracts, PsycINFO, Cumulative Index for Nursing and Allied Health Literature, Cochrane Reviews and Trials, Social Science Citation Index (1985–November

2013), British Nursing Index (1994–November 2013), and Applied Social Science Index and Abstracts (1987–November 2013).

The PICOS method (participants, interventions, comparisons, outcomes, and study design) [21] was used to define the research question, inclusion and exclusion criteria, and to develop the database search strategy. Search terms were grouped into five themes based on this method: topic of interest (e.g. error, ME[s]); measuring error rate (e.g. rate); stage of medication use process (e.g. drug administration); study design (e.g. randomized controlled trial [RCT]), and study setting (e.g. hospital). A complete example of the search strategy for EMBASE is available in the Electronic Supplementary Material. Search terms underwent slight modification depending on which database was used. Whilst the reference lists of included studies and relevant review articles identified from the search were examined to identify additional publications, study authors were not contacted for this information. All searching was carried out electronically; no hand searching of paper journals was conducted.

2.2 Inclusion and Exclusion Criteria

Studies published in any language between 1985 and November 2013 reporting on the impact of any intervention(s) on the rate of MAEs (all types or a proportion, e.g. clinically significant) and/or related ADEs (actual or potential patient harm resulting from MAEs) in the hospital setting were sought; this included both ward- and theatre-based studies, as it was felt that despite differences in the nature and design of workflow between these environments, transferable lessons may be learned in relation to medication administration. Data reported outside commercial publishing were not searched. Theses and conference proceedings were excluded, as was research carried out in patients' own/nursing/care homes, primary care, or outpatient clinics. Studies needed to compare outcome rates between an intervention and a comparator group in order to be eligible for inclusion; comparator groups were defined as either those that did not receive any intervention or those that received an alternative intervention. Outcome rates needed to either be already reported or be calculable using raw numerator and denominator data.

RCTs and non-randomized controlled trials (CTs, including 'controlled before and after' and 'interrupted time series' designs) were eligible for inclusion according to the Cochrane Effective Practice and Organisation of Care (EPOC) Group criteria [20]; before and after studies that did not utilize a separate comparator group were excluded. Please see Table 1 for a summary of the EPOC study design inclusion criteria [20]. Review articles, studies based on simulation, and conference abstracts were excluded. No restrictions were placed upon the data collection method used by studies to identify MAEs/ADEs; instead, the review team critically evaluated the suitability of each method.

2.3 Data Extraction

The following information was independently extracted from each eligible study by two authors (either RNK and SDW or RNK and JC), who then met to reach consensus: core details (e.g. date, authors, setting), study background details (e.g. sampling strategy, data collection method, definitions), and outcome measures. If required, study authors were contacted for additional data.

2.4 Definitions

An MAE was defined as 'a deviation from the prescriber's medication order as written on the patient's medication chart, the manufacturers' instructions, or relevant institutional policies' [5]. Ward-level medication preparation and dispensing errors were included, whilst prescribing and pharmacy dispensing errors were not. ADEs were defined as injuries resulting from medication use; these may be considered as potential ADEs (with little harm potential) or actual preventable ADEs (harm associated) [3]. Interventions were defined as 'the implementation of any measure designed to impact on the rate of MAEs or related ADEs in hospitals.'

2.5 Data Analysis

Studies were grouped and findings presented after data extraction according to the emerging intervention themes of 'medication use technology', 'ward system changes', 'nurse education and training', and 'changing practice in anesthesia'. Due to the heterogeneity of study objectives, designs, methods, and outcome measures, data were analysed separately for each study, with changes in outcome rates between study groups compared using the risk ratio (RR) with 95 % confidence interval (CI), calculated using OpenEpi software [22]. Two authors (RNK and SDW or RNK and JC) independently assessed risk of bias for each study according to the EPOC Group criteria [23]. A third author (DMA) made the final recommendation in any cases of disagreement.

3 Results

3.1 Search Process

Thirteen studies were included, consisting of six RCTs and seven CTs. A total of 14,640 articles were excluded at the

Table 1 EPOC study design inclusion criteria

Randomized controlled trials
Individuals, providers, or groups are allocated randomly to one or more alternative interventions
Non-randomized controlled trials
An experimental study in which people are allocated to different interventions using non-random methods
Controlled before and after studies
Outcomes are measured before and after an intervention is introduced in both control and intervention groups
Interrupted time series
A study using observations made at multiple time points both before and after implementation of an intervention (i.e. the interruption)

title review stage as they were either duplicates or did not report on medication safety topics. Abstracts were then removed if they did not focus on interventions to reduce MEs. Following this, full texts of the remaining articles were examined and removed if they did not report on MAE/related ADE rates associated with such interventions in the hospital setting. These included a number of studies that did not focus on MAE/ADEs or provide rates or relevant outcome data ($n = 44$) and those study designs not meeting the inclusion criteria ($n = 48$). No foreign language studies met the inclusion criteria. Reference list examination included review articles focusing on MEs that were referenced in the introduction, which were either identified from the literature search or from prior knowledge [8, 14, 17, 18]. A summary of the search process is shown in Fig. 1.

3.2 Study Characteristics

3.2.1 Country of Origin and Date of Publication

The majority of studies ($n = 6$, 46.1 %) originated from the USA [24–29]. Two were from New Zealand (15.4 %) [30, 31], and the remainder originated from France [32], the UK [33], Canada [34], Australia [35], and Vietnam

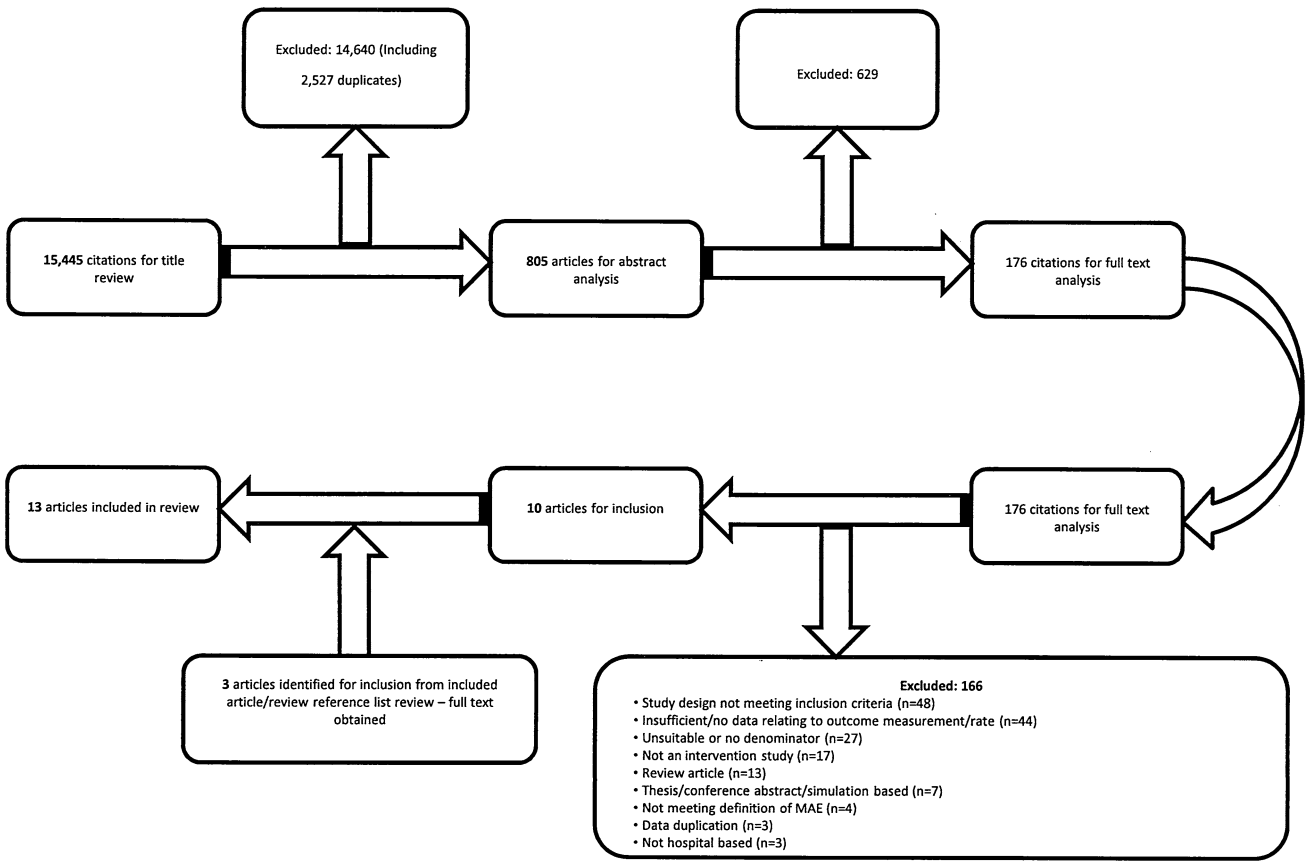

Fig. 1 Summary of citation identification and exclusion process

Table 2 Summary of study characteristics

Study, year of publication, country	Setting	Pts	Aim	Description of intervention	Study period	Design	Allocation method	Sampling strategy	Staff studied	Data collection method	Data collector	Error review strategy
Kruse et al. [35], 1992, Australia	H: geriatric rehab and assessment unit (3 wards)	A	Single nurse drug admin vs. two nurse (standard practice)	Dual nurse drug admin policy suspended. At least one registered nurse involved in dual admin, single nurse admin must be RN	46 wks	RCT—crossover design and separate control ward	NS	NS	RNs and NS nurse type	CR and SR	NS researcher	NS
Bates et al. [24], 1998, USA	H: surgical and medical ICU, 2 medical, 2 surgical wards	A	CPOE vs. CPOE plus multi-faceted team intervention	Team intervention: developed by MDT, included pharmacist role change, standardized labeling, dilutions chart introduction, communication log, and drip rate calculation program	16 mo	RCT	NS (wards matched then randomized)	Random using number generator	Nurses, pharmacists, medical and clerical staff	CR and SR and solicited reports	NS investigator	2 blinded physicians reviewed errors for severity status or exclusion, met for consensus, IRR provided
Dean and Barber [33], 2000, UK	H: 1 vascular surgery, 1 medical renal ward	A[a]	PODs scheme vs. traditional drug supply system	Use of pts own med during H stay (bedside locker used for storage)	34 days (expected)	CT	NA	NS	Nurses	DO	2 pharmacists	MDT assessed error severity
King et al. [34], 2003, Canada	H: 3 medical, 2 surgical wards	P	CPOE vs. handwritten prescriptions	Eclipsys system without decision support or pharmacy system integration (linked with laboratory)	6 y	CT	NA	NS	Nurses and physicians	SR	SR Nurses and physicians	2 physician reviewers reassessed severity, IRR provided
Greengold et al. [25], 2003, USA	2 H: 4 medical or surgical wards (H1), 4 med-surg ward (H2)	A	Dedicated med nurses vs. conventional general nurses	Med nurses attended 1-day med safety course. On specified working days, med nurses admin all scheduled med (with some exceptions)	12 wks	RCT	Random number generator	NS	Nurses	DO	H1: 2 nurses, H2: 2 pharmacy technicians	NS
Rothschild et al. [29], 2005, USA	H: 2 cardiac surgery ICU, 2 cardiac surgery step-down units	A	Smart pumps with integrated decision support vs. without decision support software	New IV infusion pumps introduced. Collected data during periods where new real-time decision support feature switched on (2 × 8 wks) vs. when switched off (2 × 8 wks). Each period separated by 2 wks	32 wks of data collection (16 control, 16 intervention) with 2-wk gaps between each phase	CT	NA	Randomization of time periods[a] All pts admitted during study period	Nursing and anesthesia staff	CR and SR, computerized ADE surveillance monitor, solicited reports and infusion pump logs	Research nurses, SR, pump log reports	2 independent physician reviewers judged AE severity and preventability using Likert scales. Disagreements resolved by discussion

Table 2 continued

Study, year of publication, country	Setting	Pts	Aim	Description of intervention	Study period	Design	Allocation method	Sampling strategy	Staff studied	Data collection method	Data collector	Error review strategy
Schneider et al. [26], 2006, USA	3 H: medical or med-surg wards	A	Educational CD ROM vs. standard practice	Interactive CD ROM program 'Basic med admin' covering principles of safe admin, pt allergies, communication, ME reporting, and managing physician orders	6 wks	RCT	Random number generator	NS	Nurses	DO	2 NS Observers	NS
Paoletti et al. [27], 2007, USA	H: 2 cardiac telemetry, 1 med-surgical	A[a]	eMAR + BCMA vs. standard practice	Nurse uses handheld scanner to scan pt wristband and drug product label to confirm admin. Includes use of eMAR system	~1 y	CT	NA	NS	Nurses	DO	4 nurses	NS
Ford et al. [28], 2010, USA	H: 1 medical ICU, 1 coronary ICU	A	Education sessions: didactic lecture vs. Simulation-based training	Material delivered based on results of baseline error observations Simulation: human-pt simulator that responded to mistakes (e.g. heart rate) to assess admin technique Lecture: admin technique, common problems, and error consequences	Baseline period followed by two 4-wk follow-up periods	CT	NA	NS	Nurses	DO	2 pharmacists	2 blinded critical care pharmacists reviewed errors (full role NS)
Webster et al. [30], 2010, NZ	2 H: all operating rooms	A + P[a]	Multifaceted system vs. traditional practice	New anesthesia admin system based on human factors principles (large, clear label lettering with barcode; standardized color-coded labels and trolley; computerized alerts; barcode scanner; workspace reorganization; pre-filled syringes; automated anesthetic record)	5 y, 9 mo	CT	NA	NS how hospitals chosen. All anesthetics included	Anesthetists	SR	SR anesthetist	NS
Chapuis et al. [32], 2010, France	H: 2 medical ICU	A	ADS vs. standard practice	OmniRx ADS: computer-controlled drug storage and dispensing unit. Compartments reloaded daily by pharmacy technician	2 mo per ICU per phase	RCT	Computerized random number generator	Purposive sampling[a]	Nurses	DO	1 pharmacist	Independent blinded MDT assessed for error stage, type, and severity
Merry et al. [31], 2011, NZ	H: 5 operating theatres	A	Multifaceted system vs. traditional practice	As above for Webster et al. [30]	1 y	RCT	Computer-generated random sequence by wk	Purposive sampling	Specialist and trainee anesthetists	MR	NS Observer	4 blinded anesthetists for dose discrepancies only

Table 2 continued

Study, year of publication, country	Setting	Pts	Aim	Description of intervention	Study period	Design	Allocation method	Sampling strategy	Staff studied	Data collection method	Data collector	Error review strategy
Nguyen et al. [36], 2014, Vietnam	H: 1 ICU, 1 post-surgical unit	A[a]	Assess effect of a clinical pharmacist-led training program on clinically relevant IV MAEs	Educational program targeting wrong preparation and admin technique errors: 2 × 30-min lectures, 1 × 45-min practical session, guidelines/posters developed by clinical pharmacist and chief nurse	84 h per ward per phase	CT	NA	NS	Nurses	DO	4 blinded pharmacy student observers	4 blinded MDT assessed clinical relevance of identified IV MAEs

A adults, *ADE* adverse drug event, *admin* administration/administered, *ADS* automated ward-based dispensing system, *AE* adverse event, *BCMA* barcode-assisted medication administration, *CD-ROM* compact disc read only memory, *CPOE* computerized physician order entry, *CR* chart review, *CT* non-randomized controlled trial, *DO* direct observation, *eMAR* electronic medication administration record, *H* hospital, *ICU* intensive care unit, *IRR* inter-rater reliability, *IV* intravenous, *MAE* medication administration error, *MDT* multi-disciplinary team, *ME* medication error, *med* medication, *MR* medicines reconciliation, *NA* not applicable, *NS* not specified, *P* pediatrics, *POD* patient's own drugs, *pt(s)* patient(s), *RCT* randomized controlled trial, *RN* registered nurse, *SR* self-report, *wk* week, *y* year

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[36]. Two studies [24, 35] were published prior to the year 2000. Study characteristics are summarized in Table 2.

3.2.2 Setting and Demographics

Two studies were carried out across two hospitals [25, 30] and one across three institutions [26]. The majority ($n = 10$) of studies included medical, surgical, and/or intensive care settings [24, 28, 29, 32, 36], with one also including step-down units [29]. Two papers were focused solely on operating theatres [30, 31] and another on geriatric assessment and rehabilitation [35].

Eleven studies focused only on adult patients, one pediatrics [34], and another all age groups [30]. The majority ($n = 8$) of studies investigated outcomes resulting solely from the actions of nursing staff, with the remainder anesthetists ($n = 2$), a combination of these groups [29], or not stating whether nurses had sole responsibility for administration [24, 34].

3.2.3 Intervention(s)

Two studies compared the impact of two different interventions on MAEs without including a 'standard practice' comparator group (though baseline measurements were included) [24, 28]. The remaining 11 studies assessed the effect of an intervention against standard practice. The interventions were heterogeneous in nature, but clustered around four main themes: medication use technology ($n = 4$); nurse education and training ($n = 3$); changing practice in anesthesia ($n = 2$); and ward system changes ($n = 4$). Individual intervention descriptions can be found in Table 2.

3.2.4 Study Design

Six studies were RCTs [24–26, 31, 32, 35] and the remainder were CTs. Most RCTs used random number/sequence generators [25, 26, 31, 32]. Two studies did not describe the method of randomization [24, 35]. One CT mentioned randomization in the abstract but the authors later stated in the discussion that an RCT was not possible [29].

Outcome data collection techniques varied between studies, with the most commonly used being direct observation ($n = 7$). Three studies reported use of multiple data collection techniques, which included chart review and incident report review in all, amongst others [24, 29, 35].

In four studies, data collection was disguised so that subjects were not aware of the study purpose [25, 33, 34, 36]. In three studies, data collection was undisguised [26, 30, 31], with the details not specified in the remaining six studies [24, 27–29, 32, 35].

Based on study design, the intervention being tested and author reporting, data collectors were considered not blinded to study aims and comparator groups (except for three studies [26, 34, 36]). Blinding of data collectors was not clear in one study [35]. Six studies described a training process for their data collectors (one said only that they were trained [29]) [25–28, 31, 36], and only two studies reported some form of measure of consistency between observer measurements (where more than one was used) [28, 31].

Seven studies described a process to review the error data [24, 28, 29, 31–33, 36]. Two studies described a process of re-grading confirmed MEs [29, 34]. There was little consistency in which professional groups carried out these assessments. In all but two studies [29, 34], the assessor(s) were reported as blinded and three studies reported the use of a statistical measure of consistency between the data generated by those asked to carry out the assessments [24, 29, 34].

3.2.5 Definitions

Six studies [24, 28, 29, 32, 35, 36] used referenced criteria [37–43] to supplement their own formal/working definition of a MAE/ADE, with considerable variation seen in the definitions reported. The majority of studies ($n = 7$) reported their own definition, either stated formally or as a working definition, with no referenced criteria [25–27, 30, 31, 33, 34]. Of these, the majority described MAEs as a discrepancy between the physician order and what was observed during administration processes [25–27, 33], which broadly matches the frequently used definition from Allan and Barker [5, 44].

Significant variation was seen in which subcategories of MAEs/related potential or preventable ADEs were reported by the included studies (e.g. timing errors, wrong dose). Three studies did not specify any outcome subcategories [24, 30, 34], and the number reported by the remaining studies varied considerably.

3.3 Outcome Measures

The majority of studies reported data on the number of MAEs ($n = 11$) [25–28, 30–36]. Of these, three also sought to determine the potential [32] or actual [36] severity of identified errors (one study simply reported whether MAEs caused harm or not [31] and in another study this was not stated [33]). The denominator 'total opportunities for error' was most commonly used ($n = 6$) [25–27, 32, 33, 36], and can be defined as the number of doses administered (whether correct or incorrect) plus those omitted [44]. Other measures included MAEs and/or related potential/preventable ADEs per 1,000 patient days [24, 34], number of doses administered [28, 31, 35], per 100 patient-pump days [29], and number of self-reported anesthetic forms returned [30]. Key outcome data from the included studies are shown in Table 3.

3.4 Impact of Interventions

3.4.1 Medication Use Technology

Three technological interventions demonstrated significant reductions in outcome rates between control and intervention groups post-intervention as shown in Table 4 [27, 32, 34]. However, although most studies provided baseline outcome data only a study investigating an automated ward dispensing system (ADS) tested for differences in outcome rates at baseline [32]. Different baseline outcomes and characteristics between study wards represented a high risk of potential bias when investigating barcode medication administration (BCMA) (see Table 5 for potential bias risk assessments) [27]. This study was given a potentially unclear bias risk for selective outcome reporting, as some results were presented without being described in the methods [27]. Despite positive findings in the observation-based ADS study, sample size did not meet pre-specified targets [32]. One study comparing the effect of turning on decision support-enabled pump software and when it was switched off found that serious MAEs (preventable ADEs and non-intercepted potential ADEs) were not reduced when using a combination of non-observation-based data collection methods [29]. One potential limitation of this study was the risk of learning bias amongst staff introduced through alternating exposure between intervention and control periods [29]. The study investigating the effect of computerized physician order entry (CPOE) utilized a retrospective design involving incident report numerator data and, like other technological interventions, allocation bias was scored as high risk, as participants were likely to know which intervention they used in comparison with their colleagues [34].

3.4.2 Ward System Changes

Introducing nurses dedicated to the administration of medication significantly increased the MAE rate compared with general nurses in one RCT using direct observation (RR 1.63, 95 % CI 1.42–1.87) [25]. Initiation of a patient's own drugs (PODs) scheme in one hospital did not change the observed MAE rate in a CT using a before and after design; however, dissimilar wards were compared [33]. One RCT reported no difference in ADE rates between CPOE and CPOE plus a multifaceted team-based intervention (RR 0.91, 95 % CI 0.49–1.67) though both

Table 3 Summary of main outcome measures

Theme and sub-theme (study design)	Data collection method	Numerator/ denominator	Error number (phase/ group)	Denominator value	Rate	Error number (phase/group)	Denominator value	Rate	Error number (phase/ group)	Denominator value	Rate	Error number (phase/ group)	Denominator value	Rate
Medication use technology														
ADS [32] (RCT)	DO	Numerator: MAEs Denominator: TOE, DOE (data shown are TOE)	58 (pre control)[a]	300[a]	19.3[a]	75 (pre int)[a]	368[a]	20.4[a]	62 (post control)[a]	333[a]	18.6[a]	64 (post int)[a]	475[a]	13.5[a]
BCMA + eMAR [27] (CT)	DO	Numerator: MAEs Denominator: TOE	60 (pre control)	306	19.6	128 (pre int)	628	20.4	63 (post control)	306	20.6	92 (post int)	628	14.6
Smart pump with decision support [29] (CT)	CR + SR + solicited reports + PL + ADE monitor	Numerator: pADEs/ potADEs Denominator: 100 pt-pump days	87 (no decision support)	4,276	2.0	93 (decision support)	3,869	2.4						
CPOE [34] (CT)	Staff SR	Numerator: MAEs Denominator: 1,000 pt days	177 (pre control)	50,659	3.49	137 (pre int)	38,578	3.6	210 (post control)	51,660	4.1	80 (post int)	38,286	2.1
Ward system changes														
Med nurse vs. general nurse [25] (RCT)	DO	Numerator: MAEs Denominator: TOE	253 (general nurses)	3,661	6.9	651 (med nurses)	5,792	11.2						
CPOE vs. CPOE plus team int [24] (RCT)	CR + SR + solicited reports	Numerator: pADEs/ potADEs Denominator: 1,000 pt days	50 (baseline)	12,218	4.1	21 (CPOE + team)	13,304	1.6	20 (CPOE)	11,235	1.8			
Dual vs. single nurse admin. [35] (RCT)	CR + SR	Numerator: MAEs Denominator: doses administered	63 (ward A dual nurse)	23,109	0.27	29 (ward B dual nurse)	20,319	0.14	41 (ward A single nurse)	20,733	0.20	79 (ward B single nurse)	19,542	0.40
PODs scheme [33] (CT)	DO	Numerator: MAEs Denominator: TOE	43 (pre control)[a]	1,071[a]	4.0[a]	66 (pre int)	1,510	4.4	43 (post control)[a]	995[a]	4.3[a]	64 (post int)	1,279	5.0
Nurse education and training														
CD ROM education program [26] (RCT)	DO	Numerator: MAEs Denominator: TOE	17 (pre control)	266	6.4	20 (pre int)	301	6.6	14 (post control)	284	4.9	25 (post int)	285	8.8
Didactic vs. simulated learning [28] (CT)	DO	Numerator: MAEs Denominator: doses administered	48 (pre sim)	156	30.8	33 (pre didactic)	159	20.8	12 (post sim)	246	4.9	93 (post didactic)	319	29.2
Pharmacist-led training [36] (CT)	DO	Numerator: clinically significant MAEs Denominator: TOE	151 (pre int)	236	64.0	162 (pre control)	280	57.9	199 (post int)	407	48.9	180 (post control)	281	64.1

Table 3 continued

Theme and sub-theme (study design)	Data collection method	Numerator/ denominator	Error number (phase/ group)	Denominator value	Rate	Error number (phase/group)	Denominator value	Rate	Error number (phase/ group)	Denominator value	Rate	Error number (phase/ group)	Denominator value	Rate
Changing practice in anesthesia														
Multi-faceted initiative [31] (RCT)	MR	Numerator: MAEs Denominator: doses administered	13 (conv)	5,084	0.26	9 (new system)	5,680	0.16						
Multi-faceted initiative [30] (CT)	Staff SR	Numerator: MAEs/ near misses Denominator: anesthetic forms returned	88 (conv – hosp A)	19,427	0.45	58 (new system)	8,666	0.67	180 (conv – hosp B)	31,180	0.58			

[a] Data obtained from author correspondence

ADE adverse drug event, *ADS* automated ward dispensing system, *BCMA + eMAR* barcode medication administration + electronic medication administration record, *CD ROM* compact disc read only memory, *Conv* conventional, *CPOE* computerized physician order entry, *CR* chart review, *CT* non-randomized controlled trial, *DO* direct observation, *DOE* detailed opportunity for error, *Int* intervention, *MAE* medication administration error, *Med* medication, *MR* medicines reconciliation, *PL* pump logs, *pADE* preventable ADE, *PODs* pts own drugs, *potADE* potential ADE, *Pre* pre-intervention, *Post* post-intervention, *pt* patient, *RCT* randomized controlled trial, *Sim* simulated, *SR* self-report, *TOE* total opportunity for error

interventions were associated with reductions in outcome rates when compared with combined baseline data [24]. A crossover RCT demonstrated that single nurse administration was associated with more MAEs than dual nurse (RR 1.41, 95 % CI 1.07–1.85); however, significant differences in rates were seen between wards when fixed at either dual or single nurse administration, and the control unit also showed a substantial decrease in MAE rate between phases [35]. Data were also presented differently than reported in the methods by this study, raising the potential risk for selective outcome reporting [35]. In two studies, contamination bias was potentially high, as participants were likely to have been exposed to both control and intervention practices [25, 35].

3.4.3 Nurse Education and Training

When an interactive compact disc read-only memory (CD-ROM) program to improve administration practices was evaluated using an RCT design with direct observation, MAE rates were found to not change significantly (and showed a trend towards an increased rate) at post-intervention when compared with standard practice (RR 1.78, 95 % CI 0.94–3.35) [26]. However, these results may be viewed cautiously, as denominator numbers did not meet the pre-defined sample size. In contrast, a CT comparing didactic with simulation-based nurse education interventions on MAE rates, again using direct observation, found a statistically significant reduction for simulated learning (RR 0.17, 95 % CI 0.09–0.30) [28]. A second direct observation-based CT, which compared a control ward with a unit whose nurses had undergone lectures and a practice-based training program in IV dose preparation and administration (along with introducing and advertising an IV dosing policy), also reported positive results for the intervention for both clinically significant IV MAEs (RR 0.76, 95 % CI 0.67–0.87) and when all MAEs were combined [36]. Unlike other studies where high potential contamination bias risks were noted, two of these studies utilized blinded data collectors, and all three involved interventions that were not outwardly visible unless the nurse revealed their allocation, thus having a low potential bias risk [26, 28, 36].

3.4.4 Changing Practice in Anesthesia

An RCT and CT investigating a multifaceted system in anesthesia, which included electronic administration and redesign of drug trays/drawers and labels, failed to demonstrate a significant reduction in MAEs per doses administered (RR 0.62, 95 % CI 0.27–1.45) [31] or self-report forms returned (RR 1.26, 95 % CI 0.95–1.68) [30]. One CT was also conducted across apparently dissimilar

Table 4 Summary of risk ratios with 95 % confidence intervals

Theme	Intervention	Study design	Description	RR value	95 % CI
Medication use technology	ADS vs. standard practice	RCT [32]	Intervention vs. control post intervention phase	**0.72**	**0.53–1.00**
	BCMA + eMAR vs. standard practice	CT [27]	Intervention vs. control post phase	**0.71**	**0.53–0.95**
			Intervention vs. control pre phase	1.04	0.79–1.37
	Smart infusion pump with real-time decision support vs. no decision support software	CT [29]	No decision support vs. decision support	1.18	0.88–1.57
	CPOE vs. standard practice	CT [34]	Intervention vs. control post phase	**0.51**	**0.40–0.66**
			Intervention vs. control pre phase	1.02	0.81–1.27
Ward system changes	Medication nurse role vs. general nurse role	RCT [25]	Medication nurse vs. general nurse	**1.63**	**1.42–1.87**
	CPOE plus multifaceted team intervention vs. CPOE	RCT [24]	CPOE + team intervention vs. CPOE alone	0.89	0.48–1.64
	Single vs. double nurse drug administration	RCT [35]	1 vs. 2 nurse administration	**1.41**	**1.07–1.85**
	PODs scheme vs. standard practice	CT [33]	Intervention vs. control post phase	1.12	0.79–1.69
			Intervention vs. Control pre phase	1.09	0.75–1.59
Nurse education and training	Self-directed educational CD ROM program vs. standard practice	RCT [26]	Intervention vs. control post phase	1.78	0.94–3.35
	Didactic vs. simulated ward-based learning	CT [28]	Simulation vs. didactic post phase	**0.17**	**0.09–0.30**
			Simulation vs. didactic pre phase	**1.48**	**1.01–2.18**
	Clinical pharmacist-led training program vs. standard practice	CT [36]	Intervention vs. control post phase	**0.76**	**0.67–0.87**
			Intervention vs. control pre phase	1.11	0.96–1.27
Changing practice in anesthesia	Multifaceted initiative vs. standard practice	RCT [31]	SAFERSleep® vs. traditional system	0.62	0.27–1.45
	Multifaceted initiative vs. standard practice	CT [30]	SAFERSleep® vs. traditional system	1.26	0.95–1.68

ADS automated ward-based dispensing system, *BCMA* barcode assisted medication administration, *CD ROM* compact disc read only memory, *CI* confidence interval, *CPOE* computerized physician order entry, *CT* non-randomized controlled trial, *eMAR* electronic medication administration record, *POD* patients own drugs, *RCT* randomized controlled trial, *RR* risk ratio

RR and 95 % CI which appear in bold are statistically significant ($p < 0.05$)

settings without comparing them [30]. These two studies were considered at high risk of potential contamination bias, as participating staff had either used the intervention before the study [31] or were likely to have been exposed to both control and intervention knowledge, technology, or practice [30, 31].

4 Discussion

This is the first systematic review with a focus on evaluating the impact of interventions designed to reduce the rate of MAEs and related ADEs in hospitals. Key strengths of this review are the time period covered and the use of established approaches to apply inclusion criteria and undertake independent risk of bias assessments, which have been used in a previous systematic review assessing the effect of interventions on ADEs [45]. Whilst it is important to recognize the contribution of well known research outside this review in working towards reducing the MAE burden such as other BCMA evaluations [46], our inclusion criteria were designed to identify studies where changes in outcome rates could be compared against a comparator group to help mitigate against contamination or changes in outcome independent of an intervention, which are important sources of potential research design bias.

Study settings varied considerably amongst the included studies (e.g. intensive care [ADS] vs. medical/surgical wards [BCMA, CPOE]), which is important to consider when taking account of the external validity of the findings presented [1, 5, 6]. Analysis of comparator groups also revealed important differences in outcome rates between study sites and individual units, a phenomenon commonly encountered in MAE research [5]. Study authors have suggested that these differences may arise due to medicines management activities, staff roles, or workload factors unique to each ward [25, 27]. In one study, results from all included wards were grouped together to present findings, which may mask important changes in outcomes [29]. These findings highlight the importance of using similar study units where possible and reporting data from all included groups.

The variety of outcome definitions used by studies included in this review has been reported elsewhere as an

Table 5 Summary of potential bias risk assessment

Study, year of publication	Risk of bias assessment (EPOC)								
	Allocation sequence generation	Allocation concealment	Baseline outcome measures similar	Baseline characteristics similar	Incomplete data adequately addressed[a]	Knowledge of allocated intervention prevented	Study protected against contamination	Study free from selected outcome reporting	Other potential bias risk(s)
Kruse et al. [35]	High	Low	High	High	Low	High	High	High	Change in control unit error rate. No washout between phases. No DO. NS if data reviewed. NS if data collectors trained
Bates et al. [24]	Unclear	Low	Unclear	Unclear	Low	High	Unclear	Unclear	No training for data collectors/reviewers specified
Dean and Barber [33]	High	High	Low	High	Low	High	Unclear	Low	Did not reach stated observation value for 50 % reduction in error
King et al. [34]	High	High	Low	Low	Low	High	Unclear	Low	Clinical pharmacists introduced during study phase. Stats power not described. No DO or data collector training specified
Greengold et al. [25]	Low	Low	Unclear	Low	Low	High	High	Low	Extra nurses recruited during study who were not randomized. No data review or consensus specified
Rothschild et al. [29]	High	Unclear	Unclear	Unclear	Low	High	High	Low	New infusion-pump intervention introduced shortly before commencement of study. Unclear use of randomization in study. Supported by manufacturer of pump technology
Schneider et al. [26]	Low	Low	Low	Low	Low	Low	Unclear	Low	Did not achieve 29 nurses per group for statistical power. No data review or consensus specified
Paoletti et al. [27]	High	High	High	High	Low	High	Unclear	Unclear	Statistical power calculations NS. No data review or consensus specified
Ford et al. [28]	High	Unclear	High	Low	Low	Low	Unclear	Low	Advanced IV pump system introduced during study phase
Webster et al. [30]	High	High	Unclear	High	Low	High	High	Low	May not have reached number of records required for statistical power. COI declared. No DO, data review, training, or consensus specified
Chapuis et al. [32]	Low	Low	Low	Low	Low	High	High	Low	Did not achieve 2,000. Detailed opportunities for error per group for statistical power
Merry et al. [31]	Low	Low	Unclear	Low	Low	High	High	Low	40 % emergency cases despite stating only electives included. COI declared. No DO
Nguyen et al. [36]	High	High	Low	Unclear	Low	Low	Unclear	Low	Did not formally compare data collected between observers (though training/data review mentioned)

[a] As the risk of incomplete data was considered by the reviewers to be minimal, all studies were ranked 'low risk'

COI conflict of interest, *DO* direct observation, *EPOC* Effective Practice and Organisation of Care, *IV* intravenous, *NS* not stated

influence on reported outcome measures and a barrier to comparing results [5, 6, 8, 47]. In addition, variability in which MAE subtypes were studied and whether error severity was investigated added to this uncertainty. Despite their reported frequency in MAE research [5], timing errors were included in only four studies [26, 28, 32, 35]. A range of different reported MAE subtypes were reported in direct observation studies, which reflects the findings of a recent review [6]. Only four studies carried out an assessment of the severity of identified MAEs [31–33, 36], a finding that has been shared elsewhere when assessing direct observation-based MAE research [5]. Aside from two studies that provided enough information to determine whether harm was actual or potential [32, 36], no changes in error severity were attributed to the intervention [33] or no errors causing harm were captured [31]. Greater standardization is therefore required to address the impact of interventions on harm associated with the full range of MAEs, including whether actual or potential harm was measured [5, 6].

Direct observation is considered the most appropriate method to identify MAEs, as it identifies the largest number and full range of errors compared with chart review and self-reporting [48, 49] and does not appear to be influenced by observation time or observer intervention [50]. Whilst seven studies used direct observation for MAE data collection, one used chart review [35], another used reconciliation [31] and two others used self-reporting [30, 34] methods that may underestimate the MAE rate. The studies that detected types of ADEs using chart review and self-reporting, amongst other methods [24, 29], may not be disadvantaged as chart review is suitable for identifying such outcomes [51], though caution must be advised as different adverse event detection methods show little overlap in their findings [52].

Although a positive impact on outcomes was seen for some medication use technology, nurse educational/training and ward system interventions, equivocal or negative changes in MAE rates were seen for those that remained, some of which were assessed using RCTs with less risk of potential bias.

With the exception of decision support-enabled infusion pumps, medication use technology interventions (CPOE, ADS, BCMA/ electronic medication administration record [eMAR]) showed statistically significant reductions in outcome rates [27, 32, 34]. Of these, two used direct observation error detection methods (ADS, BCMA) [27, 32]. In particular, in the RCT design of the ADS study [32], the risk of bias was limited to contamination and allocation knowledge, which are difficult to enforce in hospitals where staff move between wards and the intervention is clearly visible and requires interaction. However, the positive outcomes reported in the CPOE study [34] should be viewed with caution given the unreliability of incident reports as a reflection of MAE rates over time, and the wider question should be asked as to whether this intervention would have a pronounced effect on MAEs beyond written communication deficiencies. Although overall these results for technology are encouraging, further research is required to confirm these findings. Future evaluations could place greater emphasis on the untoward effects of information technology on medication use processes; safety features of infusion pumps were often bypassed in one included study [29], and research conducted elsewhere suggests workarounds are a major barrier to effective implementation of medication administration support technology [13, 53] and that implementation of technology requires careful planning to avoid such issues [54].

Mixed results were observed when changes to ward systems were made. The observed increase in MAEs for single nurse medication administration warrants careful consideration, as potential risks of bias affecting almost all assessed areas were noted as well as a large decrease in MAE rate between phases for the control group [35], which may indicate the influence of other ward changes or circumstances in accounting for the change in MAE rate. One RCT with fewer potential risks of bias found that nurses made more errors when they were given the sole task of medication administration [25], and elsewhere a patients' own drugs scheme [33] and a multifaceted team intervention inferred no significant reductions in outcome rates [24].

Two studies (including one RCT) found that a multifaceted system to improve IV medication administration in anesthesia did not reduce MAEs [30, 31], though contamination and blinding were areas of high risk of potential bias and errors were measured using techniques other than direct observation, where self-reporting in particular meant that the rates of errors reported may have been influenced by awareness of errors and reporting behavior as well as the intervention being tested [55].

Direct observation evidence from nurse education and training interventions suggests that self-directed learning does not appear effective thus far in reducing MAEs in hospitals [26], but that simulation-based exercises and clinical pharmacist-led training may show promise, though further rigorous evaluation is required [28, 36]. Two studies (including one RCT) [25, 26] found that their educational/ward system changes reduced procedural errors such as failure to check or borrowing medicines but did not reduce (and displayed a trend towards increasing) MAEs. The origins of some MAEs may thus be independent of such failures [25, 26].

The educational interventions appeared practical, as they required little time for staff to participate [26, 28, 36]. In contrast, technological interventions such as BCMA/eMAR, CPOE, ADS, and the multifaceted anesthesia system may require substantial and sustained organizational change, along with major financial investment and may therefore take a considerable period of time to implement and for

benefits to be seen (as well as altering time spent on certain tasks [31]) [11, 55]. However, research has noted economic benefits associated with barcode-assisted pharmacy dispensing [56], CPOE [57], and BCMA [58]. Changing the role of nurses and patients may be less costly than technological innovations to introduce, but one must consider their impact on social dynamics and workflow patterns [25], with one study reporting that dual nurse administration took twice as long as single nurses [35]. In addition, the attitudes and experiences of front-line staff using these interventions are an important contributor to successful implementation [59], and must be evaluated more rigorously, as only two studies reporting such measures asked both comparator groups for feedback [28, 31, 32]. Although RCT study designs are preferable when evaluating interventions, they may not be feasible when testing particular patient safety research questions, or evaluating interventions that are implemented across a hospital simultaneously [60].

Whilst a number of different interventions were evaluated, other important targets for MAE minimization did not feature and warrant investigation using robust study designs [8]. These include interventions to reduce interruptions/distractions and to improve the process of medication dosing, including checking and checklists. Recent research has identified weaknesses in existing interventions designed to minimize interruptions (and MAEs) [14] and where future investigations could focus [14, 61, 62]. Others have reported that checking exercises may minimize MAEs, though more robust evaluations are needed [15, 63]. Given the frequency with which intensive care units (ICUs, $n = 5$, with two using ICUs exclusively [28, 32]) and theatres ($n = 2$) [30, 31] were used by studies in this review, one must also consider that errors may originate from different pathways and factor combinations than other environments [8, 64], which may then suggest different solutions. Evidence from critical care suggests that no single intervention can as yet be recommended, with relevant studies possessing limitations similar to those identified in this review [17]. Despite our understanding that multifaceted interventions are likely to be needed to reduce MEs [7, 8, 10], the few studies employing this approach failed to show benefits [24, 30, 31], though one study reported reductions in IV MAEs after implementing procedural and training changes, though their focus was on the latter of the two interventions [36]. This suggests that further theoretical study of their underlying causes may be required to best inform forthcoming interventions [8, 65].

5 Conclusion

The evidence base for interventions designed to reduce MAEs in hospital settings is limited. Despite this, significant improvements in MAE/related ADE rates were seen for nurse education and training initiatives, and medication use technology interventions, though these findings should be viewed with caution as many did not utilize optimal study designs or more suitable data collection techniques, and all were susceptible to potential risk of bias. Evidence from RCTs with fewer potential biases suggests that dedicated medication nurses, self-directed educational CD ROM packages on medication administration safety, and a multimodal anesthesia drug delivery package may not reduce MAEs in hospitals. In the future, greater standardization of methods and a more theory-driven approach to the design and implementation of forthcoming interventions to minimize MAEs is needed, whereby knowledge of the range and causes of these errors is used to guide their prevention.

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