Interventions to reduce medication errors in neonatal care: a systematic review

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Abstract

Background: Medication errors represent a significant but often preventable cause of morbidity and mortality in neonates. The objective of this systematic review was to determine the effectiveness of interventions to reduce neonatal medication errors.

Methods: A systematic review was undertaken of all comparative and noncomparative studies published in any language, identified from searches of PubMed and EMBASE and reference-list checking. Eligible studies were those investigating the impact of any medication safety interventions aimed at reducing medication errors in neonates in the hospital setting.

Results: A total of 102 studies were identified that met the inclusion criteria, including 86 comparative and 16 noncomparative studies. Medication safety interventions were classified into six themes: technology ($n = 38$; e.g. electronic prescribing), organizational ($n = 16$; e.g. guidelines, policies, and procedures), personnel ($n = 13$; e.g. staff education), pharmacy ($n = 9$; e.g. clinical pharmacy service), hazard and risk analysis ($n = 8$; e.g. error detection tools), and multifactorial ($n = 18$; e.g. any combination of previous interventions). Significant variability was evident across all included studies, with differences in intervention strategies, trial methods, types of medication errors evaluated, and how medication errors were identified and evaluated. Most studies demonstrated an appreciable risk of bias. The vast majority of studies (>90%) demonstrated a reduction in medication errors. A similar median reduction of 50–70% in medication errors was evident across studies included within each of the identified themes, but findings varied considerably from a 16% increase in medication errors to a 100% reduction in medication errors.

Conclusion: While neonatal medication errors can be reduced through multiple interventions aimed at improving the medication use process, no single intervention appeared clearly superior. Further research is required to evaluate the relative cost-effectiveness of the various medication safety interventions to facilitate decisions regarding uptake and implementation into clinical practice.

Keywords: intervention, medication errors, neonatal intensive care unit, newborn infant, systematic review

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Introduction

Medication errors represent a significant burden to the healthcare system.[1] They can be defined as any preventable event that can cause or lead to inappropriate medication use or patient harm and can occur at any stage in the medication-use process such as prescribing, transcribing, dispensing, administering, and monitoring of medications.[2] Neonates are more prone to medication errors at each stage of the medicine management process due to the increased need for calculations, dilutions, and manipulations of medications.[3,4] Furthermore, many medications are used off-label in the neonatal setting, meaning that they are not specifically licensed for use in neonates and are therefore often only available in adult formulations

and concentrations.[5] As a result, prescribing and administration challenges often places neonates at risk of potentially fatal 10-fold or 100-fold dosing errors.[6,7] There is also the associated challenge of limited dosing protocols and evidence-based information regarding the efficacy, safety, dosing, pharmacokinetic, and clinical use of medications in neonates.[6] In addition, relative physiological immaturity means that neonates have less capacity in being able to buffer unintended consequences of medication errors.[8] Such susceptibility towards medication errors in neonates, as previously described, is further emphasized by previous research that observed that medication errors with the potential to cause significant harm were three times more likely to occur in the neonatal intensive care unit (NICU) than in adult wards.[9] Furthermore, an analysis of all medical errors occurring within the NICU identified that medication errors were the single largest contributor, accounting for 47.2% of all errors.[10]

Given the complexity of medication use in neonates, the high frequency in which high-risk medications are used and the potential for serious adverse events of even minor medication errors, intervention strategies to increase medication safety in neonatal care should be regularly reviewed. The identification and evaluation of such interventions are of critical importance in assisting healthcare systems and providers in understanding, implementing, and augmenting interventions to reduce neonatal medication errors.[11] Despite this importance, there have been few extensive systematic reviews on interventions for preventing medication errors in the neonatal setting, with the most recent reviews only including literature up until 2013.[12–14] Further, none of these reviews included both comparative and noncomparative studies. The aim of this systematic review was to identify and review different types of interventions to reduce neonatal medication errors.

Method

Search strategy

PubMed and EMBASE were searched for any studies published from 1966 until April 2016, without any language restrictions. The search included a medication errors/safety concept and a neonatal concept, with terms entered as controlled vocabulary and as keywords in all databases. MeSH search terms included: 'medication errors' AND 'Infant, Newborn', OR 'Intensive Care Units, Neonatal', OR 'Intensive Care, Neonatal', OR 'Pediatrics'. Reference lists of all articles included in full-text review, as well as other review articles, were screened for additional studies.

Eligibility criteria

To be eligible for inclusion:

(1) An intervention specifically aimed at reducing the risk of medication errors must be carried out or reported.
(2) There must have been some measure to evaluate effectiveness in reducing risk of medication errors.
(3) The study setting must have included neonates.

Studies only published in abstract form were not eligible for inclusion.

Data abstraction

Two independent, nonblinded authors (MRN and LEG) reviewed each title and abstract for inclusion eligibility. Full-text review was also conducted by two independent, nonblinded authors (MRN and LEG) and discrepancies were resolved through author consensus discussions. For non-English language studies included in the full-text review, the primary author (MRN) translated the contents with computer translation software, which has previously been demonstrated as effective for systematic reviews.[15] The study selection process was documented as per the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA).[16] Data were collected in relation to study characteristics, intervention strategy, comparator treatment (if applicable), type of medication error evaluated, specific detail of medication error, and main study findings. Qualitative descriptors were utilized to describe the results of studies. We did not plan to perform a meta-analysis.

Study quality assessment

Study quality was evaluated by two independent reviewers (MRN and LEG) using the Cochrane Effective Practice and Organization of Care (EPOC) Review Group risk of bias tool, which evaluates all study types together including randomized controlled trials, nonrandomized trials, and controlled before–after studies utilizing the same eight criteria.[17]

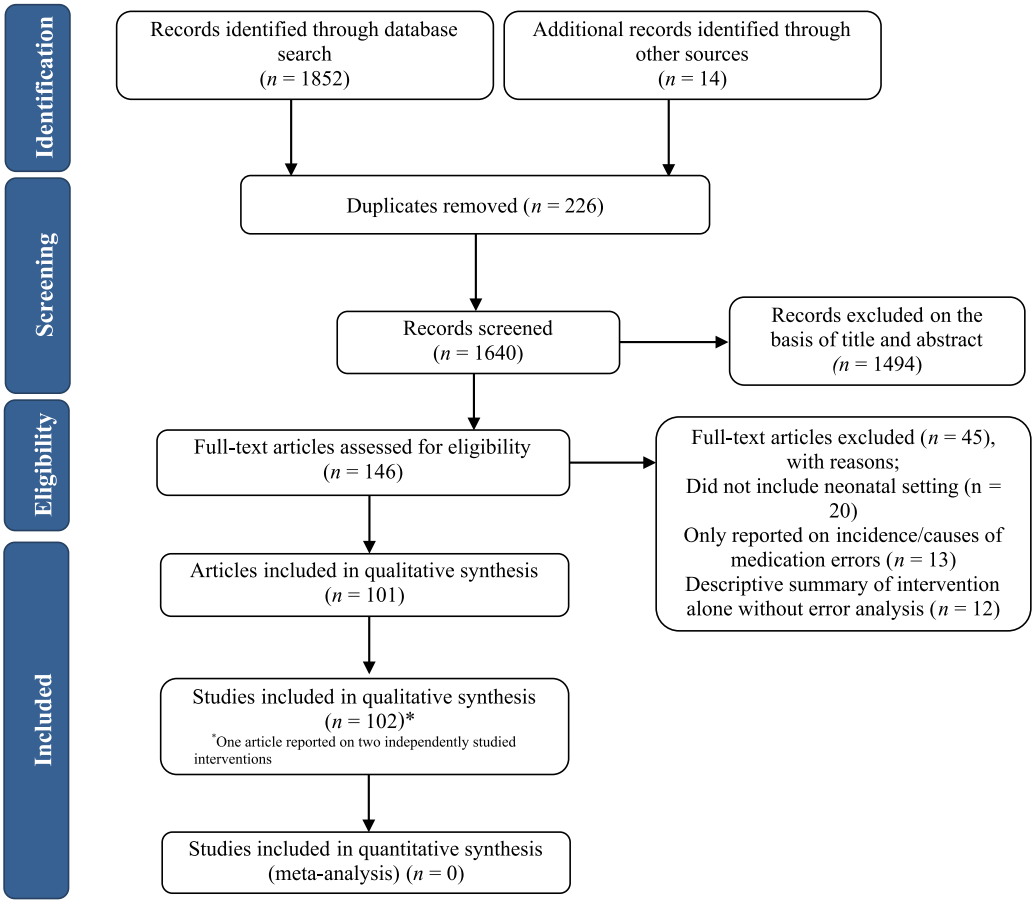

Figure 1. Flow diagram of included studies.

Results

Search results

Our search identified 1852 abstracts, 226 of which were duplicates and were removed. An additional 14 articles were identified from previous systematic reviews or from checking citations of included studies and were retrieved for full-text review, leaving a total of 1640 unique records. A total of 146 articles were included in full-text review and of these, 101 were deemed eligible for inclusion in the systematic review. One article reported separately on two independently studied interventions, resulting in a total of 102 eligible studies (Figure 1).

Overview of included studies

Identified studies were grouped according to their intervention type and are presented in Table 1, together with an example of an intervention within that group. The six intervention types included: technology (n = 38),[18–55] organizational (n = 16),[56–71] personnel (n = 13),[72–84] pharmacy (n = 9),[85–93] hazard and risk analysis (n = 8),[10,93–99] and multifactorial (i.e. a combination of any of the previous themes; n = 18).[100–117] A detailed summary of each individual study included in the review is presented in Table 2.

Of the 102 eligible studies, 86 were comparative studies and 16 were noncomparative studies (Table 3). The majority of included studies were undertaken in a combined PICU/NICU setting (n = 64; 63%). Most studies were conducted in the United States (n = 60; 59%), with 42 (41%) studies published since 2010. The majority of studies (n = 68; 66%) focused on a single medication error type, including prescribing (m = 41), administration (n = 26), or monitoring (n = 1), while the remaining 34 (33%) studies involved the investigation of multiple error types.

Risk of bias evaluation

Most studies demonstrated an appreciable risk of bias (Figure 2). The lack of randomized controlled

Table 1. Overview of identified interventions for reducing medication errors in neonatal care.

Intervention type	Example of intervention	References
Technology ($n = 38$)		
Computerized physician order entry and clinical decision support ($n = 15$)	Electronic medication prescribing and atuomated dose checking	36–50
Computerized physician order entry ($n = 5$)	Electronic medication prescribing	51–55
Clinical decision support alone ($n = 2$)	Electronic tool to verify parenteral nutrition orders	34–35
Computer programmes ($n = 8$)	Online parenteral nutrition calculator	23–30
IV administration technology ($n = 4$)	Auomated infusion devices	19–22
Barcoding ($n = 3$)	Barcode medication administration system	31–33
Organizational ($n = 16$)		
Guidelines, policies, and procedures ($n = 9$)	Development of preformatted medication order sheets	56–64
Medication distribution and supply ($n = 6$)	Preparation of prediluted medications for administration	65–70
Nurse prescribing ($n = 1$)	Transcription of paper-based orders to electronic orders by nursing staff	71
Personnel ($n = 13$)		
Staff education ($n = 13$)	Personalized feedback of medication prescribing errors	72–84
Pharmacy ($n = 9$)		
Ward based ($n = 6$)	Interventions identified through introduction of ward-based paediatric/neonatal clinical pharmacy service	85–90
Dispensary based ($n = 3$)	Interventions identified through dispensary-based pharmacy service	91–93
Hazard and risk analysis ($n = 8$)		
Quality improvement tools ($n = 4$)	Use of failure modes, effects, and criticality analyses to redesign care processes	10,95–97
Error detection tools ($n = 3$)	Automated detection of medication errors	93,98–99
Safe learning systems ($n = 1$)	Critical incident reports of medication errors	94
Multifactorial ($n = 18$)		
GPPs + education ($n = 7$)	Standardized IV infusion concentration list with intensive education programme	100–106
GPPs + education + technology ($n = 5$)	Antimicrobial stewardship programme facilitated by electronic prescribing and provision of individualized real-time feedback	107–111
GPPs + education + pharmacy ($n = 4$)	Preprinted medication order sheets with increase in clinical pharmacy services and provision of real-time feedback to prescribers on medication errors	112–115
Education + pharmacy ($n = 1$)	Pharmacist-led education programme on medication errors and daily pharmacist review of medication orders	117
Pharmacy + technology ($n = 1$)	Utilization of clinical pharmacists to review and intercept any adverse drug events and electronic prescribing	116

GPPs, guidelines, policies and procedures; IV, intravenous.

trials meant that studies were at high risk of bias across the domains related to random allocation of intervention and concealment of intervention group. Inadequate reporting or lack of accounting for differences in characteristics between the pre- and postintervention groups and nonblinding of

Table 2. Summary of study characteristics and results by primary intervention theme.

Study (country)	Study setting	Intervention type	Intervention detail	Comparator	Main type of error collected	Detail of medication error	Main finding
Technology							
Abboud *et al.*[41] (US)	N/P	CPOE + CDS	Integration of reminder for aminoglycoside monitoring into CPOE system	Pre–post	Monitoring	Failure to appropriately monitor aminoglycoside	No change in appropriate monitoring [31/177 (17.5%) *versus* 31/159 (19.5%)]
Balaguer Santamaria *et al.*[24] (Spain)	N	Calculator	Development of Neodosis, an electronic spreadsheet to assist in calculating medication doses and standardize dilutions of commonly used drugs	Calculations performed without use of calculator	Prescribing	Errors in calculation of dose	Use of electronic calculator resulted in significant reduction in number of staff making errors [19/27 (70.3%) *versus* 4/27 (14.8%); $p < 0.001$]
Boling *et al.*[40] (US)	N/P	CPOE + CDS	CPOE with dose range checking system	Pre–post	Prescribing	Dosing errors involving opioids, benzodiazepines, and potassium, requiring administration of antidote	Reduction in opioid prescribing errors [8/13,997 (0.06%) *versus* 1/7256 (0.01); $p = 0.17$], while there were no errors involving benzodiazepines or potassium in the pre- or postperiod
Brown *et al.*[30] (US)	N	Computer programme	Computerized worksheet for parenteral nutrition orders	Pre–post	Prescribing	Any prescribing errors associated with TPN orders	Reduction in errors from 44/303 (14.5%) to 12/177 (6.8%); $p = 0.016$
Cordero *et al.*[38] (US)	N	CPOE + CDS	CPOE with NICU-specific physician order sets	Pre–post	Prescribing and administration	Caffeine loading dose administration > 3 h after being prescribed and gentamicin prescribed dose > 10% deviation from recommended dose	Significant improvement in administration of caffeine within 3 h of prescription (12% *versus* 63%; $p < 0.05$), and reduction in gentamicin dosing errors from 16/136 (11.7%) to 0/117 (0%); $p < 0.05$
Farrar *et al.*[37] (US)	N/P	CPOE + CDS	CPOE system with CDS implementation	Pre–post	Prescribing	Any prescribing error	Reduction in errors from 46/103 (44.7%) orders to 7/114 (6.1%) orders ($p < 0.001$)
Ferranti *et al.*[47] (US)	N/P	CPOE + CDS	CPOE incorporating advanced dosing model	Pre–post	Any type	Any errors resulting in patient harm (e.g. transient adverse effects which required corrective therapy or increased length of stay)	Reduction in errors in NICU from 75/567 (13.2%) to 23/272 (8.5%); $p = 0.006$

Table 2. (Continued)

Study (country)	Study setting	Intervention type	Intervention detail	Comparator	Main type of error collected	Detail of medication error	Main finding
Garner *et al.*[35] (US)	N	CDS	Interactive computerized order set with decision support for antibiotic orders	Pre–post	Prescribing	Any errors in antibiotic prescribing	Overall error rate decreased from 1.7 per medication order to 0.8 per medication order ($p < 0.001$)
Hardmeier *et al.*[33] (US)	N	Barcoding	Implementation of barcode medication administration system	None	Administration	Any nursing-related administration errors	Total of 7/300 (2.3%) nursing-related administration errors reported during study period
Hennings *et al.*[20] (US)	N/P	IV administration technology	Automated infusion devices with programmed alerts	None	Administration	Alerts requiring reprogramming events 2.5 times above or below the predefined limits for high-risk medications	Total of 36/5268 infusions (0.7%) required reprogramming; reprogramming much more common in the paediatric compared with adult ICU (RR 1.68 95% CI 1.18–2.38)
Hilmas *et al.*[27] (US)	N/P	Computer programme	Computer-based order forms for parenteral nutrition ordering	Pre–post	Prescribing	Any TPN prescribing errors	Reduction in errors from 38/152 (25%) orders to 7/442 (1.6%) orders ($p < 0.01$)
Holdsworth *et al.*[43] (US)	N/P	CPOE + CDS	CPOE system with CDS implementation	Pre–post	Any type	Any error which may result in ADE (dispensing error, overdose, underdose, wrong dose	Reduction in any errors (RR 0.34; 95% CI 0.24–0.49) and serious or life-threatening errors (RR 0.23; 95% CI 0.07–0.80)
Jozefczyk *et al.*[59] (US)	N	CPOE	CPOE system implementation	Pre–post	Prescribing	Any prescribing errors	Number of orders without any prescribing errors increased from 209/500 (41.9%) to 480/500 (96%) medication orders ($p = 0.001$)

Table 2. (Continued)

Study (country)	Study setting	Intervention type	Intervention detail	Comparator	Main type of error collected	Detail of medication error	Main finding
Kadmon *et al.*[46] (Israel)	N/P	CPOE + CDS	Multistep process of introduction of CPOE, followed by introduction of CPOE + CDS	Pre–post	Prescribing	Any prescribing error	Compared with errors occurring in baseline period [103/1250 (8.2%) orders], there were significant reductions in errors occurring following the introduction of CPOE [97/1250 (7.8%) orders ($p = 0.66$)], CPOE and CDS [55/1250 (4.4%) orders ($p < 0.001$)], and further modification to CPOE and CDS system [18/1250 (1.4%) orders (<0.001)]
Kazemi *et al.*[48] (Iran)	N	CPOE + CDS	Multistep process of introduction of CPOE, followed by introduction of CPOE + CDS	Pre–post	Prescribing	Dosing errors related to antibiotic and anticonvulsant orders	Compared with errors occurring in baseline period [876/1668 (52%) orders], a similar number occurred following the introduction of CPOE alone [749/1489 (50%) orders], with a reduction following introduction of CPOE and CDS [442/1331 (33%) orders (p_{trend} <0.001)]
Kelly *et al.*[23] (US)	N/P	Computer programme	Electronic infusion calculator	Conventional calculator	Administration	Incorrect infusion rate calculation	Significant improvement in calculation accuracy from 61.9 ± 8.15% to 100 ± 0% ($p < 0.001$)
Larsen *et al.*[19] (US)	N/P	IV administration technology	Automated infusion devices with standard infusion concentrations	Pre–post	Administration	Any administration errors involving one of the standardized medications	Absolute risk reduction of 2.3 errors per 1000 medication doses (95% CI 1.1–3.4)
Lehmann *et al.*[26] (US)	N	Computer programme	Online parenteral nutrition calculator	Pre–post	Prescribing	Any TPN prescribing errors	Reduction in errors from 60/557 (10.7%) orders to 20/471 (4.2%) orders ($p < 0.001$)
Lehmann *et al.*[28] (US)	N	Computer programme	Online parenteral nutrition calculator	Pre–post	Prescribing	Any prescribing errors associated with TPN orders	Reduction in errors from 60/557 (10.7%) orders to 8/656 (1.2%) orders ($p < 0.001$)
Lehmann *et al.*[42] (US)	N/P	CPOE + CDS	Web-based calculator for IV continuous infusions	Pre–post	Prescribing	Any prescribing errors involving medication infusions	Reduction in errors from 35/129 (27%) orders to 8/142 (6%) orders ($p < 0.001$)

(Continued)

Table 2. (Continued)

Study (country)	Study setting	Intervention type	Intervention detail	Comparator	Main type of error collected	Detail of medication error	Main finding
Maat *et al.*[49] (Netherlands)	N	CPOE + CDS	Computerizing prescribing and calculating system on hypo/hyper-glycaemia	Pre–post	Prescribing	Calculation error of glucose intake	No difference in incidence of hypoglycaemia [4.0/100 hospital days (95% CI 3.2–4.8) to 3.1/100 hospital days (2.7–3.5), $p = 0.88$)] or hyperglycaemia [6.0/100 hospital days (95% CI 4.3–7.7) to 5.0/100 hospital days (3.7–6.3), $p = 0.75$]
MacKay *et al.*[50] (US)	N/P	CPOE + CDS	Electronic ordering and compounding system for parenteral nutrition	Pre–post	Any type	Any errors involved in prescribing, transcribing, preparation, and administration of TPN	Reduction from 15.6/1000 orders to 2.7/1000 orders ($p < 0.001$)
Manrique-Rodriguez *et al.*[21] (Spain)	N/P	IV administration technology	Automated infusion devices with programmed alerts	None	Administration	Compliance with drug library	After 9 months of implementation, overall compliance with the drug library was 85%, with 94% of nursing staff recommending the introduction of this technology in other units
Manrique-Rodriguez *et al.*[22] (Spain)	N/P	IV administration technology	Automated infusion devices with programmed alerts	None	Administration	Compliance with drug library, and smart-pump programming errors	Overall user compliance 78%, leading to interception of 92 errors (from 486,875 programming events; 0.02%) of which 42% of intercepted errors were considered to be catastrophic
Menke *et al.*[25] (US)	N/P	Computer programme	Computerized clinical documentation system	Pre–post	Administration	Medication administration delay (difference between scheduled administration times *versus* actual administration time)	Increase in medication administration delay from 8.5 ± 27.9 min to 16.9 ± 34.9 min ($p < 0.01$)
Morriss Jr *et al.*[31] (US)	N	Barcoding	Barcode medication administration system	Pre–post	Administration	Any nursing-related administration errors	Reduction in likelihood of preventable ADE (HR 0.53; 95% CI 0.29–0.91)
Morriss Jr *et al.*[32] (US)	N	Barcoding	Barcode medication administration system	Pre–post	Administration	Any nursing-related administration errors	Reduction in likelihood of preventable ADE (HR 0.48; 95% CI 0.23–0.98)

Table 2. (Continued)

Study (country)	Study setting	Intervention type	Intervention detail	Comparator	Main type of error collected	Detail of medication error	Main finding
Myers *et al.*[36] (US)	N	CPOE + CDS	CPOE system with CDS implementation	Pre–post	Any type	Any error leading to adverse drug reaction report	Reduction in errors from 3.2 to 0.6 per 1000 patient days
Peverini *et al.*[34] (US)	N	CDS	Graphic user interface for parenteral nutrition decision support	Pre–post	Prescribing	Any TPN prescribing errors	Reduction in errors from 62/266 (23.3%) orders to 0/290 (0%) orders ($p < 0.001$)
Potts *et al.*[39] (US)	N/P	CPOE + CDS	CPOE system with CDS implementation	Pre–post	Prescribing	Any prescribing errors	Reduction in errors from 2662/6803 (39.1%) orders to 110/7025 (1.6%) orders ($p < 0.001$)
Russell *et al.*[18] (US)	N/P	CPOE + computer programmes	CPOE with bidirectional interface between pharmacy and CPOE systems for infusion-pump orders	Pre–post	Prescribing and administration	Any error related to prescribing or administration of infusions	Reduction in errors with IV fluids from 97/231 to 46/152 orders ($p = 0.01$), with smaller reduction in errors with medication (72/296 to 54/303 orders; $p = 0.05$)
Skouroliakou *et al.*[29] (Greece)	N	Computer programme	Computer-assisted parenteral nutrition ordering programme	Pre–post	Prescribing	Any prescribing errors associated with TPN orders	Reduction in errors from 28/941 (3%) orders to 0/941 (0%) orders ($p < 0.001$)
Taylor *et al.*[52] (US)	N	CPOE	CPOE system implementation	Pre–post	Administration	Any administration errors	Reduction in errors from 50/253 (20%) administration episodes to 31/268 (12%) administration episodes (RR 0.53 95% CI 0.33–0.84)
Trotter and Maier[53] (Germany)	N/P	CPOE	CPOE system implementation	Pre–post	Prescribing	Any prescribing errors involving parenteral nutrition or IV medications	Reduction in errors from 484/4118 (12%) orders to 3/5480 (0.1%) orders ($p < 0.001$)
Upperman *et al.*[51] (US)	N/P	CPOE	CPOE system implementation	Pre–post	Any type	Any error leading to possible or actual ADE	No reduction in total errors from 0.3 ± 0.04/1000 doses to 0.37 ± 0.04/1000 doses ($p = 0.3$), but reduction in harmful ADEs from 0.05 ± 0.017/1000 doses to 0.03 ± 0.003 doses ($p = 0.05$)
Vardi *et al.*[44] (Israel)	N/P	CPOE + CDS	CPOE system with CDS implementation	Pre–post	Prescribing	Any prescribing errors related to resuscitation medication orders	Reduction in errors from 3/13,124 (0.02%) orders to 0/46,970 (0%) orders

(Continued)

Table 2. (Continued)

Study (country)	Study setting	Intervention type	Intervention detail	Comparator	Main type of error collected	Detail of medication error	Main finding
Walsh *et al.*[45] (US)	N/P	CPOE + CDS	CPOE system with CDS implementation	Pre–post	Any type	Any error leading to potential or actual patient harm	No difference in serious medication errors from 31.7/1000 patient-days to 33.0/1000 patient-days (IRR 1.04; 95% CI 0.70–1.54) with slight reduction in errors causing patient harm from 7.9/1000 patient-days to 6.5/1000 patient-days (IRR 0.83; 95% CI 0.37–1.87)
Warrick *et al.*[54] (UK)	N/P	CPOE	CPOE system implementation	Pre–post	Prescribing and administration	Any prescribing and administration errors	Reduction in prescribing errors from 14/159 (9%) orders to 12/257 (5%) orders ($p = 0.09$) and administration errors from 43/528 (8%) to 4/278 (1%) orders ($p < 0.05$)
Organizational							
Aguado-Lorenzo *et al.*[70] (US)	N	Medication distribution and supply	Preparation of ready-to-use morphine infusion from pharmacy	Morphine infusions prepared on ward by nurses	Administration	Deviation (>7.5%) from labelled concentration	Number of infusions outside of acceptable concentration limits lower among those prepared by pharmacy compared with those prepared on the ward by nurses [19/99 (19.2%) *versus* 9/115 (7.8%); $p = 0.015$]
Allegeart *et al.*[68] (US)	N	Medication distribution and supply	Use of paediatric amikacin vials (50 mg/ml)	Preparation of doses from adult-strength vials (250 mg/ml)	Administration	Inability to achieve target plasma concentrations/ pharmacokinetic parameters	Achievement of target concentrations higher with use of paediatric vial compared with adult-strength vial [40/56 (72%) *versus* 44/75 (58%); $p = 0.132$]
Broussard *et al.*[59] (US)	N/P	GPPs	Implementation of preformatted order sheets with dosing instructions and sedation monitoring form	Pre–post	Prescribing	Any prescribing errors (e.g. wrong dose, units) relating to sedatives	Reduction in medication-ordering errors, including using units/kg ($p < 0.05$), ordering of the appropriate reversal agent ($p = 0.02$), and correct medication dosage ($p < 0.001$)
Conroy[69] (US)	N/P	Medication distribution and supply	Use of medications licensed for use in paediatrics	Unlicensed/ off-label medication use	Any type	All medication errors identified by clinical staff	Unlicensed/off-label medication use in neonates associated with more medication errors (OR 5.81; 2.32–14.55)

Table 2. (Continued)

Study (country)	Study setting	Intervention type	Intervention detail	Comparator	Main type of error collected	Detail of medication error	Main finding
Hilmas *et al.*[62] (US)	N	GPPs	Parenteral nutrition prescribing process	None	Prescribing	Any prescribing and transcribing errors related to parenteral nutrition orders	Prescribing process demonstrated 50–60% compliance with recommended standards, while pharmacist interventions were made for 5% of orders
Kazemi *et al.*[71] (Iran)	N	Nurse prescribing	Transcription of order by nurse into electronic prescribing programme	Physician order directly into electronic prescribing programme	Prescribing	Any errors related to use of antibiotics or anticonvulsants	Involvement of nurses in prescribing resulted in reduction in medication errors (RR 0.50; 0.50–0.71)
O'Brodovich and Rappaport[66] (Canada)	N/P	Medication distribution and supply	Unit dose drug distribution system	Pre–post	Administration	Any administration errors	Observed medication incident rates decreased from 10.3% to 2.9% ($p < 0.05$) and the nurses' time spent on medication-related activities decreased from 23.7% to 21.6%
Olsen *et al.*[65] (Denmark)	N/P	Medication distribution and supply	Implementation of a satellite pharmacy incorporating unit dose drug distribution	Pre–post	Administration	Any administration errors	Introduction of satellite pharmacy led to overall increase in errors from 389/856 (45%) to 280/540 (52%; $p = 0.020$), but a reduction in serious errors from 66/856 (7.7%) to 0/544 (0%; $p < 0.05$)
Palmero *et al.*[64] (Switzerland)	N	GPPs	Implementation of preformatted order sheets	Pre–post	Prescribing	Any error related to prescribing identified by pharmacist review of all medication orders	Significant reduction in prescribing errors [146/505 (28.9%) *versus* 71/525 (13.5); $p < 0.05$]
Roman[57] (US)	N/P	GPPs	Standardized infusion concentrations (SC)	None	Administration	Any administration-related errors	In the 2 years since the implementation of SC, only five medication errors involving medication administration were identified

(Continued)

Table 2. (Continued)

Study (country)	Study setting	Intervention type	Intervention detail	Comparator	Main type of error collected	Detail of medication error	Main finding
Ross *et al.*[56] (UK)	N/P	GPPs	Introduction of pharmacy dispensing double-check; education of nursing staff regarding IV administration; nonpunitive error reporting policy	Pre–post	Any type	Any reported medication errors	Introduction of double checking policy with pharmacy dispensing led to reduction in medication errors from 9.8 per year to 6 per year. Introduction of increased education of nursing staff regarding IV administration led to reduction in medication errors from 37 per year to 32 per year. Change in error reporting form to make it less punitive increased the error reporting rate from 33 per year to 38 per year
Sturgess *et al.*[60] (UK)	N/P	GPPs	Implementation of zero-tolerance prescribing policy incorporating a dedicated prescribing area and daily feedback of prescribing errors	Pre–post	Prescribing	Any error related to prescribing (e.g. wrong drug, dose, frequency)	Reduction in prescribing errors from 969/1111 patient days (87%) to 796/1781 patient days (45%) ($p < 0.001$)
Thomas *et al.*[61] (UK)	N	GPPs	Introduction of standardized gentamicin pathway for prescribing and monitoring	Pre–post	Administration	Errors related to gentamicin administration and monitoring (e.g. not given within 60 min of scheduled dose, inappropriate action take after level results)	Introduction led to significant improvement in number of doses given within 60 min of scheduled dosing time (82% *versus* 73%; $p = 0.02$), documentation of gentamicin level (78% *versus* 62%; $p = 0.04$), appropriate action taking according to level result (77% *versus* 61%; $p = 0.04$), and documentation of length of gentamicin therapy (61% *versus* 42%; $p = 0.045$)
Valizadeh *et al.*[63] (Iran)	N	GPPs	Preparation of oral solutions using tablets	Target oral solution strength	Administration	Accuracy of prepared dose concentration for spironolactone and captopril prepared oral solutions	Significant differences and variability in prepared oral solution strength compared with the prescribed dose. The difference was statistically significant for captopril (0.35 $\pm$ 0.41 mg; $p < 0.001$), but not spironolactone (0.23 $\pm$ 1.58 mg; $p = 0.26$)

Table 2. (Continued)

Study (country)	Study setting	Intervention type	Intervention detail	Comparator	Main type of error collected	Detail of medication error	Main finding
Watanachai *et al.*[67] (Thailand)	N	Medication distribution and supply	Use of needle nonremovable syringes for preparation of medication dilutions	Use of needle removable syringes	Administration	Inaccuracy in preparation of insulin infusion compared with prescribed dose	Compared with target concentration of 300 μU/ml, preparation of infusion using needle nonremovable syringes was most accurate (335 ± 28 μU/ml) compared with the use of needle removable syringes [Terumo(R) 540 ± 54 μU/ml; Nipro(R) 617 ± 45 μU/ml)
White *et al.*[58] (US)	N/P	GPPs	Introduction of mandatory medication request form for potassium chloride	Pre–post	Prescribing	Post-infusion elevation of serum potassium > 4.35 mmol/l	Significant reduction in errors from 103/1341 (7.7%) to 0/150 (0%); $p < 0.001$
Personnel							
Alemanni *et al.*[77] (Canada)	N/P	Education	Education to nursing staff regarding medication process including drug verification, preparation, and administration	Pre–post	Administration	Any nursing errors in medication preparation and administration process	Increase in overall compliance with all steps of the medication administration process from 23/142 (16%) administration episodes to 39/140 (28%) administration episodes ($p = 0.021$)
Campino *et al.*[74] (Spain)	N	Education	Comprehensive preventive educational strategy delivered by pharmacist on medication errors	Pre–post	Prescribing	Any prescribing errors	Reduction in errors from 868/4182 (21%) orders to 47/1512 (3%) orders ($p < 0.001$)
Chedoe *et al.*[82] (Netherlands)	N	Education	1 h theoretical teaching session to nurses, individual practical teaching session of commonly used medications; guided pharmacy tour	Pre–post	Administration	Any preparation and administration errors	Reduction in errors from 151/311 (49%) administration episodes to 87/284 (31%) administration episodes ($p < 0.001$)
Eisenhut *et al.*[80] (UK)	N/P	Education	Personalized assessment and feedback for medical trainees	Pre–post	Prescribing	Any prescribing errors	Reduction in total errors from 188/421 patients to 120/588 patients ($p < 0.05$) and reduction in major errors from 36/421 patients to 35/588 patients ($p < 0.001$)

(Continued)

Table 2. (Continued)

Study (country)	Study setting	Intervention type	Intervention detail	Comparator	Main type of error collected	Detail of medication error	Main finding
Gordon *et al.*[81] (UK)	N/P	Education	E-learning resources for paediatric prescribing for trainee doctors	No access to e-learning resource	Prescribing	Total score on prescribing assessment	Intervention associated with higher mean score on prescribing assessment at 4 weeks (79 ± 12.1 *versus* 63 ± 13.5) and 12 weeks (79 ± 10.1 *versus* 69 ± 12.4; $p < 0.001$) postintervention
Leonard *et al.*[73] (US)	N/P	Education	Educational website with competency examination; distribution of a personal digital assistant-based standardized dosing reference; zero-tolerance policy for incomplete/incorrect orders; prescriber performance feedback; publicizing of error/data	Pre–post	Prescribing	Any prescribing errors	Absolute risk reduction in errors of 38/100 orders written ($p < 0.001$)
Ligi *et al.*[78] (France)	N	Education	Continuous incident reporting and subsequent educational interventions to combat identified errors	Pre–post	Any type	Any error leading to patient harm	Reduction in incidence of severe errors from 7.6 to 4.8 per 1000 patient-days ($p = 0.005$), as well as reduction in 10-fold dosing errors from 2.3/100 admissions to 0.6/100 admissions ($p = 0.022$)
Munoz Labian *et al.*[72] (Spain)	N	Education	Education programme regarding common medication errors occurring within the neonatal unit	Pre–post	Prescribing	Any prescribing errors	Reduction in illegible orders from 22% to 8% ($p = 0.005$), missing route of administration from 28% to 5% ($p < 0.001$) and missing dose calculation from 54% to 22% ($p < 0.001$); no change in dosing errors from 4% to 4%

Table 2. (Continued)

Study (country)	Study setting	Intervention type	Intervention detail	Comparator	Main type of error collected	Detail of medication error	Main finding
Niemann *et al.*[84] (US)	N/P	Education	Multifaceted intervention including: provision of information on common medication preparation errors; training course on error prevention and drug handling; and provision of a comprehensive reference book	Pre–post	Administration	Any preparation error	Overall frequency of errors decreased from 527/581 (91%) administration episodes to 116/441 (26%) administration episodes ($p < 0.001$)
Raja Lope *et al.*[75] (Malaysia)	N	Education	Education programme regarding medication administration process for nursing staff	Pre–post	Administration	Noncompliance to 10 standard medication administration steps	Reduction in medication administration errors from 59/188 (31%) to 26/169 (15%) administration episodes ($p < 0.001$)
Sagy[76] (US)	N/P	Education	Education programme on medication prescribing for residents and nursing staff	Pre–post	Prescribing	Any prescribing error	Reduction in errors from 533/256 orders (2.1/order) to 38/140 orders (0.3/order); $p < 0.05$
Sullivan *et al.*[79] (US)	N/P	Education	Interactive online nursing educational module on reducing insulin administration errors	Pre–post	Administration	Administration errors involving insulin (e.g. wrong dose, incorrect documentation, inadequate monitoring following dose)	Reduction in errors from 131/882 (15%) episodes to 19/119 (2%) episodes ($p < 0.001$)
Sullivan *et al.*[83] (US)	N	Education	Personalized performance feedback of prescribing errors	Pre–post	Prescribing	Any prescribing error involving opioids and antibiotics	Reduction in opioid related errors by 83%, with increase in number of days between opioid prescribing errors from 3.94 days to 22.63 days; no change in number of days between antibiotic prescribing errors (averaged 2.14 days)

(Continued)

Table 2. (Continued)

Study (country)	Study setting	Intervention type	Intervention detail	Comparator	Main type of error collected	Detail of medication error	Main finding
Pharmacy							
Condren *et al.*[86] (US)	N/P	Pharmacy service	Paediatric clinical pharmacy service	None	Any type	All actual or potential medication errors requiring pharmacist intervention	4605 interventions performed for 3978 patients with 223 adverse drug events or medications errors prevented or detected during the study period
Folli *et al.*[92] (US)	N/P	Pharmacy service	Dispensary-based pharmacy service	None	Prescribing	Errors in medication order (e.g. wrong drug, dose, frequency, route, illegible order, drug–drug interaction, drug–disease interaction)	Overall error rates for the two hospitals were 1.35 and 1.77 per 100 patient-days, and 4.9 and 4.5 per 1000 medication orders, respectively
Gibson *et al.*[91] (UK)	N/P	Pharmacy service	Dispensary-based pharmacy service	Pre–post	Prescribing	Errors in medication order (e.g. wrong drug, dose, frequency, route, illegible order, drug–drug interaction, drug–disease interaction)	No significant reduction in prescribing errors (53/439 (12%) *versus* 46/441 (10%); $p = 0.577$)
Kaushal *et al.*[87] (US)	N/P	Pharmacy service	Ward-based paediatric clinical pharmacy service	Pre–post	Any type	Any actual or potential medication errors relating to prescribing, transcribing, dispensing, administering, or monitoring	Reduction in medication errors from 29/1000 patient-days to 6/1000 patient-days ($p < 0.01$)
Khan *et al.*[90] (India)	N	Pharmacy service	Ward-based paediatric clinical pharmacy service	None	Any type	All actual or potential medication errors requiring pharmacist intervention	Medication errors identified in 80 of 150 patients; total of 87 interventions made, with 60 accepted by clinician
Krupicka *et al.*[85] (US)	N/P	Pharmacy service	Ward-based paediatric clinical pharmacy service	None	Any type	All actual or potential medication errors requiring pharmacist intervention	A total of 172 recommendations made for 77 of 215 patients, equivalent to 35 recommendations per 100 patient-days

Table 2. (Continued)

Study (country)	Study setting	Intervention type	Intervention detail	Comparator	Main type of error collected	Detail of medication error	Main finding
Takata *et al.*[93] (US)	N/P	Pharmacy service	Dispensary-based pharmacy service	None	Prescribing	Errors in medication order (e.g. wrong drug, dose, frequency, route, illegible order, drug–drug interaction, drug–disease interaction)	A total of 2.67 (95% CI 2.4–3.0) interventions per 1000 patient-days and 0.82 (0.73–0.91) interventions per 1000 medication orders; 12% (8.8–15.9%) of interventions occurred in NICU
Tripathi *et al.*[89] (US)	N/P	Pharmacy service	Ward-based paediatric clinical pharmacy service	None	Any type	All actual or potential medication errors requiring pharmacist intervention	Total of 27,773 interventions related to 10,963 admissions, with 22,765 (80%) interventions resulting in change in therapy or monitoring
Zhang *et al.*[88] (China)	N/P	Pharmacy service	Ward-based paediatric clinical pharmacy service	None	Any type	All actual or potential medication errors requiring pharmacist intervention	Interventions resulted from a total of 31 medication errors identified from 683 prescriptions (4.5%)
Hazard and risk analysis							
Apkon *et al.*[95] (US)	N/P	Quality improvement tools	Redesign of medication infusion ordering; preparation; and administration process	Pre–post	Prescribing and administration	Failure mode effects analysis (FMEA) for severity (S), likelihood of error occurrence (O), likelihood that failures will escape detection (D) before causing harm RPN (risk priority number $= S \times O \times D$) assigned	According to FMEA analysis, changes in process led to significant reduction in criticality index associated with the following processes: prescribing the correct rate (136 to 26), calculating the correct amount of medication to prepare infusion (234 to 49), preparation of infusion (314–88), programming of infusion pump (269 to 99)
Bonnabry *et al.*[96] (Switzerland)	N/P	Quality improvement tools	Use of failure modes; effects, and criticality analysis (FMECA) to improve TPN production process	Pre–post	Prescribing and manufacturing	Any errors related to parenteral nutrition from prescribing to manufacture	Significant 59% reduction in criticality index for TPN production process from 3415 to 1397
Frey *et al.*[94] (Switzerland)	N/P	Safe learning systems	Use of critical incident reporting to implement changes to prevent medication errors	None	Any type	Any real or potential harm resulting from errors in the medication management process	A total of 284 critical incident reports were made over a 12-month process, with suggestions to prevent such future incidents provided in 62% of reports; overall, 46 critical incident reports were followed by system changes

(Continued)

Table 2. (Continued)

Study (country)	Study setting	Intervention type	Intervention detail	Comparator	Main type of error collected	Detail of medication error	Main finding
Li *et al.*[98] (US)	N	Error detection tool	Automated detection of adverse events and medical errors	Voluntary incident reporting	Prescribing and administration	Errors related to narcotic dosing and administration	18 errors identified through automated detection, only one of which was identified through voluntary incident reporting or use of a trigger tool with PPV of 39–100%
Li *et al.*[99] (US)	N	Error detection tool	Automated detection of medication administration errors	Voluntary incident reporting	Administration	Errors related to administration of incorrect dose compared with prescription	Similar specificity (98.2% *versus* 100%), but much greater sensitivity (82.1% *versus* 5.5%) and precision (70.2% *versus* 50.0%) than incident reporting for error recognition
Suresh *et al.*[10] (US)	N	Quality improvement tools	Numerous safety projects including education/training; use of FMEA; improving preparation and administration, etc.	None	Any type	Any real or potential harm resulting from errors in the medication management process	Multisite sharing of critical incident reports useful in identifying common medication errors occurring in the NICU setting
Takata *et al.*[93] (US)	N/P	Error detection tool	Use of electronic trigger tool	Voluntary incident reporting	Any type	Any injury, large or small, caused by the use (including nonuse) of a medication	Use of trigger tool identified more ADEs than voluntary incident reports (22.3/1000 *versus* 1.7/1000; $p < 0.001$), with a positive predictive value of 4.7% (3.7–5.8%)
Arenas Villafranca *et al.*[97] (Spain)	N	Quality improvement tools	Use of failure modes; effects; analysis and development of checklist to improve TPN production process	Pre–post	Prescribing and manufacturing	Any errors related to parenteral nutrition from prescribing to manufacture	Use of FMEA identified a total of 82 possible failures; the development of a checklist to address potential failures reduced mean criticality index from 137 to 48 for each item

Table 2. (Continued)

Study (country)	Study setting	Intervention type	Intervention detail	Comparator	Main type of error collected	Detail of medication error	Main finding
Multifactorial							
Abstoss *et al.*[111] (US)	N/P	GPPs; education; technology	Seven overlapping interventions including: poster tracking of errors; performance metric display in staff lounge; multiple didactic curricula; unit-wide emails summarizing medication errors; CPOE; introduction of unit-based pharmacy technicians; and patient safety report form streamlining	Pre–post	Any type	Any real or potential harm resulting from errors in the medication management process	Reported error rate increased from 3.16/10,000 to 3.95/10,000 dispensed doses ($p = 0.09$); errors causing harm reduced from 0.56/10,000 to 0.16/10,000 doses dispensed ($p < 0.001$)
Alagha *et al.*[115] (Egypt)	N/P	GPPs; education; pharmacy	New structured medication order chart; physician education; provision of dosing guide; and physician performance feedback	Pre–post	Prescribing	Any prescribing error	Reduction in errors from 1107/1417 to 391/1097 (78.1% *versus* 35.6%; $p < 0.001$)
Booth *et al.*[104] (UK)	N/P	GPPs; education	Application of prescribing guidelines with a zero-tolerance policy; providing feedback and education	Pre–post	Prescribing	Any prescribing errors	Reduction from 892/1000 to 447/1000 errors per occupied bed days ($p < 0.001$)
Bullock *et al.*[100] (US)	N/P	GPPs; education	Development ; dissemination and implementation of standardized IV infusion concentration list; intensive education and one-on-one coaching and mentoring	Pre–post	Administration	Any preparation or administration errors involving parenteral medications	Reduction in percentage of IV infusion orders that did not have standardized IV concentration used from 31/120 (26%) to 17/128 (13%), as well as reduction in associated medication errors related to improper dose from 26/50 (52%) to 7/28 (25%) and reduction in medication errors related to improper concentration from 6/26 (23%) to 0/7 (0%)

(Continued)

Table 2. (Continued)

Study (country)	Study setting	Intervention type	Intervention detail	Comparator	Main type of error collected	Detail of medication error	Main finding
Burmester *et al.*[102] (US)	N/P	GPPs; education	Post-cardiac surgery admission prescription forms; systematic physician education; publicizing error rates	Pre–post	Prescribing	Any prescribing error	Reduction in errors from 613/3648 to 366/8929 (16.8% *versus* 4.1%; $p < 0.001$)
Campino *et al.*[106] (Spain)	N	GPPs; education	Protocol standardization and educational programme consisting of theoretical and practical teaching session	Pre–post	Administration	Calculation errors (i.e. dose drawn up *versus* prescribed dose), or accuracy errors (i.e. theoretical concentration *versus* actual concentration) in preparing IV medications	Reduction in calculation errors from 6/444 to 0/291 (1.35% *versus* 0%; $p = 0.086$) and accuracy errors from 243/444 to 61/291 (54.7% *versus* 23%; $p < 0.001$)
Cimino *et al.*[112] (US)	N/P	GPPs; education; pharmacy	Various interventions delivered across different sites including: preprinted order sheets; provision of real-time feedback to prescribers on medication errors; improving availability of dosing guides; increase in pharmacist staffing; publicizing medication errors	Pre–post	Prescribing	Any prescribing error	Reduction in errors from 3259/12,026 to 217/9187 (27.9% *versus* 23.7%; $p < 0.001$) and reduction in harmful errors from 16/12,026 to 3/9187 (0.13% *versus* 0.03%)
Costello *et al.*[113] (US)	N/P	GPPs; education; pharmacy	Multiple interventions introduced over two phases including: introduction of a clinical pharmacist; paediatrics clinical pharmacist-led medication safety team; new incident reporting form and educational forums	Pre–post	Any type	Any errors	Significant increase in number of errors reported, while errors identified as being severe reduced from 46% to 8% and then 0% over each phase

Table 2. (Continued)

Study (country)	Study setting	Intervention type	Intervention detail	Comparator	Main type of error collected	Detail of medication error	Main finding
Davey *et al.*[103] (UK)	N/P	GPPs; education	Junior doctor prescribing tutorial and introduction of a bedside prescribing guideline	Pre–post	Prescribing	Dose >10% deviation from guideline or good prescribing practices not followed	Prescribing tutorial associated with reduction in errors from 76/249 to 44/266 (30.5% *versus* 16.5%; $p = 0.023$) but no further reduction with subsequent implementation of bedside guideline [59/320 (18.4%) to 56/330 (17.0%) $p = 0.73$]
Di Pentima *et al.*[109] (US)	N/P	GPPs; education; technology	Development of antimicrobial stewardship programme on vancomycin utilizing CPOE + CDS together with provision of individualized real-time feedback	Pre–post	Prescribing	Incorrect vancomycin order according to clinical indications, microbiology data or dosing guidelines	Reduction in errors from 1.8/1000 patient days to 1.4/1000 patient days ($p < 0.05$)
Hilmas *et al.*[110] (US)	N/P	GPPs; education; technology	Development of standardized approach to deliver continuous infusions; CPOE + CDS with standardized concentrations; smart-pump infusions and intensive educational sessions	Pre–post	Prescribing and administration	Incorrect continuous infusion syringe concentration, incomplete and illegible orders; incorrect administration rate and dose	Reduction in errors from 98/200 to 0/200 (49% *versus* 0%)
Irwin *et al.*[107] (Canada)	N/P	GPPs; education; technology	Standardizing infusion concentrations; CDS to assist with drug concentration and infusion rate; competency evaluation of staff with provision of educational programme	Pre–post	Any type	Any errors reported through incident monitoring programme involving parental medications	No change in errors from 2.4/year to 2.0/year
Martinez-Anton *et al.*[105] (Spain)	N/P	GPPs; education	Standardizing of dosing guidelines; pocket tables with dosing guidelines; updated protocols; education programme on correct prescribing	Pre–post	Prescribing and administration	Any medication error related to prescribing or administration (e.g. wrong medication, frequency, route, dose)	Reduction in errors from 761/2228 to 388/1791 (34.2% *versus* 21.7%; $p < 0.001$)

(Continued)

Table 2. (Continued)

Study (country)	Study setting	Intervention type	Intervention detail	Comparator	Main type of error collected	Detail of medication error	Main finding
Otero *et al.*[114] (Argentina)	N/P	GPPs; education; pharmacy	Positive safety culture with nonpunitive management of medication errors; active interaction with pharmacists during ward rounds; provision of education regarding medication prescribing and administration	Pre–post	Prescribing and administration	Any medication error related to prescribing or administration (e.g. wrong medication, frequency, route, dose)	Reduction in errors related to prescribing, from 102/590 to 105/1144 (17% *versus* 9%; $p < 0.05$) and administration from 150/1174 to 99/1588 (13% *versus* 6%; $p < 0.05$)
Pallás *et al.*[108] (Spain)	N	GPPs; education; technology	Education regarding good prescribing practice; implementation of a pocket personal computer-based automatic calculation system	Pre–post	Prescribing	Any medication error related to prescribing (e.g. wrong medication, frequency, route, dose)	Reduction in errors from 2498/6320 to 171/1435 (39.5% *versus* 11.9%; $p < 0.001$)
Simpson *et al.*[117] (UK)	N	Education; pharmacy	Pharmacist-led education programme; daily pharmacist review of medication orders; competency assessment of all neonatal unit staff; and greater publicizing of medication errors	Pre–post	Prescribing and administration	Any medication error related to prescribing or administration (e.g. wrong medication, frequency, route, dose)	Reduction in errors from 24.1/1000 to 5.1/1000 patient-days ($p = 0.037$)
Wang *et al.*[116] (US)	N/P	Pharmacy; technology	Utilization of clinical pharmacists to review and intercept any adverse drug events and CPOE	None	Any type	Any error within the medication process	Total of 865 errors identified, of which 178 considered potentially harmful; clinical pharmacists intercepted 96/178 (54%) errors, while the addition of a CPOE had the potential to intercept 130/178 (73%) errors
Yamanaka *et al.*[101] (Brazil)	N/P	GPPs; education	Redevelopment of the nursing administration process; provision of nursing education regarding medication errors; provision of dosing guidelines	Pre–post	Prescribing and administration	Any medication error related to prescribing or administration (e.g. wrong medication, frequency, route, dose)	Reduction in errors from 1717/8152 to 1498/8550 (29% *versus* 22%; $p < 0.001$)

ADE, adverse drug event; CDS, clinical decision support; CI, confidence interval; CPOE, computerized physician order entry; GPPs, guidelines, policies, and procedures; HR, hazard ratio; ICU, intensive care unit; IRR, incident rate ratio; IV, intravenous; N, neonatal only; NICU, neonatal intensive care unit; N/P, neonatal and paediatric; OR, odds ratio; PICU, paediatric intensive care unit; PPV, positive predictive value; RR, relative risk; TPN, total parenteral nutrition.

Table 3. Aggregate data synthesis for included studies by comparator status.

Characteristic	Number of studies (%)		
	Total (*n* = 102)	Comparative (*n* = 86)	Noncomparative (*n* = 16)
Location of study			
Argentina	1 (1)	1 (1)	0
Brazil	1 (1)	1 (1)	0
Canada	3 (3)	3 (3)	0
China	1 (1)	0	1 (6)
Denmark	1 (1)	1 (1)	0
Egypt	1 (1)	1 (1)	0
France	1 (1)	1 (1)	0
Germany	1 (1)	1 (1)	0
Greece	1 (1)	1 (1)	0
India	1 (1)	0	1 (6)
Iran	3 (3)	3 (3)	0
Israel	2 (2)	2 (2)	0
Malaysia	1 (1)	1 (1)	0
Netherlands	2 (2)	2 (2)	0
Spain	9 (9)	7 (8)	2 (13)
Switzerland	3 (3)	2 (2)	1 (6)
Thailand	1 (1)	1 (1)	0
UK	9 (9)	9 (10)	0
US	60 (59)	49 (57)	11 (69)
Year			
1970–1979	1 (1)	1 (1)	0
1980–1989	2 (2)	1 (1)	1 (6)
1990–1999	3 (3)	3 (3)	0
2000–2009	54 (53)	47 (55)	7 (44)
⩾2010	42 (41)	34 (40)	8 (50)
Patient location			
NICU only	38 (37)	34 (40)	4 (25)
NICU/PICU	64 (63)	52 (60)	12 (75)
Intervention theme			
Technology	38 (37)	34 (40)	4 (25)
Multifactorial	18 (18)	17 (20)	1 (6)
Organizational	16 (16)	14 (16)	2 (13)
Personnel	13 (13)	13 (15)	0

(Continued)

Table 3. (Continued)

Characteristic	Number of studies (%)		
	Total (n = 102)	Comparative (n = 86)	Noncomparative (n = 16)
Pharmacy	9 (9)	2 (2)	7 (44)
Hazard and risk analysis	8 (8)	6 (7)	2 (13)
Individual type of intervention			
CPOE ± CDS	20 (20)	20 (23)	0
Education	13 (13)	13 (15)	0
GPPs	9 (9)	7 (8)	2 (13)
Pharmacy services	9 (9)	2 (2)	7 (44)
IV administration technology	4 (4)	1 (1)	3 (19)
Electronic computer programmes	7 (7)	7 (8)	0
Medication distribution and supply	6 (6)	6 (7)	0
Barcoding	3 (3)	2 (2)	1 (6)
CDS	2 (2)	2 (2)	0
Quality improvement tools	4 (4)	3 (3)	1 (6)
Error detection tool	3 (3)	3 (3)	0
Multifactorial	18 (18)	17 (20)	1 (6)
Other	4 (4)	3 (3)	1 (6)
Types of medication errors collected			
Prescribing	41 (40)	38 (44)	3 (19)
Administration	26 (25)	21 (24)	5 (31)
Monitoring	1 (1)	1 (1)	0
Multiple types	34 (33)	26 (30)	8 (50)

Abbreviations: CDS, clinical decision support; CPOE, computerized physician order entry; GPPs, guidelines, policies, and procedures; NICU, neonatal intensive care unit; PICU, paediatric intensive care unit; IV, intravenous.

the assessment of the primary outcome were the main areas of inconsistent bias. A number of studies had unclear risk of bias for incomplete outcome data due to the fact that the outcome was reliant on voluntary incident reports from staff rather than detailed review.

Qualitative synthesis

A breakdown of medication error reduction according to intervention types and medication error types within each intervention theme is presented in Table 4. Based on a qualitative synthesis of comparative studies, the greatest median reduction in overall medication errors was seen with the use of technology-based interventions (73% reduction; n = 33 studies), but this ranged widely from an increase in medication errors of 11% to a decrease in medication errors of 100%. The remaining intervention types produced a similar reduction of medication errors of approximately 50–60%, but again, with a wide range in results.

Eight studies [consisting of a combination of technology- (n = 4), personnel- (n = 2), organizational- (n = 1), and multifactorial-based (n = 1) interventions] reported separately on minor

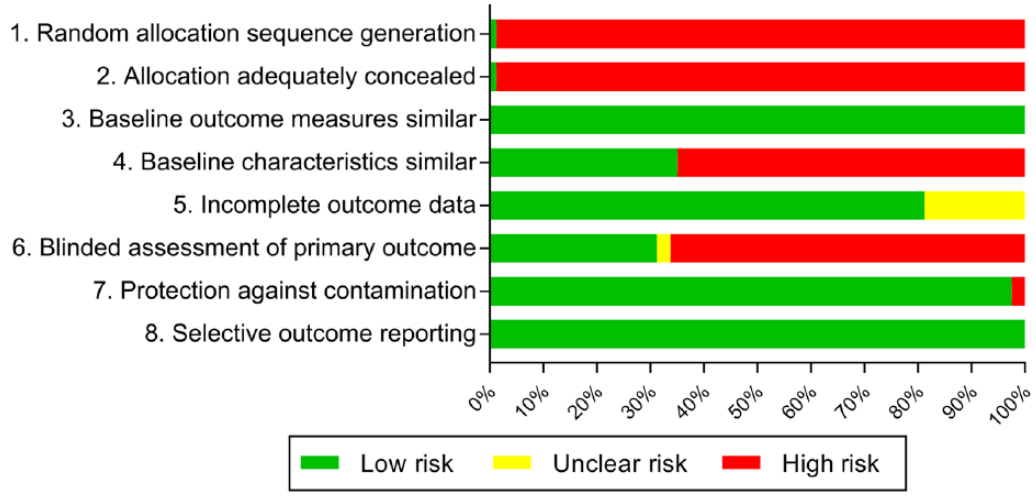

Figure 2. Risk of bias of included studies.

and major medication errors.[38,43,45,51,65,78,80,112] Among these studies, the median reduction in medication errors was notably greater for major (76%; 17–100%) compared with minor (26%; −16–66%) medication errors. Notably, one of the studies identified a 16% increase in minor medication errors following the intervention, but a substantial 100% reduction in major errors.[65] The corresponding median reduction in medication errors for any intervention was similar for those undertaken in a neonatal-only (56%; 25–100%) or combined neonatal/paediatric (66%; −16–100%) setting. Similarly, median reduction in medication errors for any intervention was similar regardless of whether errors were identified by incident reports (50%; 17–100%) or detailed medication order review (60%; −16–100%).

Discussion

Based on the findings of our review, no single intervention appeared clearly superior in reducing the risk of medication errors, with significant variability evident among studies within and across themes with respect to methods, definitions, and outcomes. Identified interventions often targeted different aspects of the medication management process, highlighting that a combination of interventions is most likely required to achieve a significant reduction in medication errors.

Santesteban and colleagues have published the most recent systematic review on interventions for preventing medication errors in neonatal care.[14] They restricted their search to studies undertaken in the neonatal unit setting only, identifying a total of 16 intervention studies published up until 2013. Our search was much more extensive, identifying 34 comparative studies undertaken in the neonatal setting, out of our total of 86 comparative studies included in this review. Despite this discrepancy in number of studies, the findings remain similar in that while many interventions demonstrated significant potential for reducing medication errors, no firm conclusions could be drawn as to which interventions were most effective. Our findings are also similar to that of an earlier systematic review by Rinke and colleagues that included 63 studies across both neonatal and paediatric settings,[12] as well as a recent Cochrane review that included findings from just seven studies.[13] Both of these reviews observed that the inability to draw firm conclusions was partly due to limited studies in some areas, while also due to significant methodological heterogeneity evident across studies. Further, a consistent issue raised across reviews is whether decreases in medication errors truly relate to benefits for patients in terms of reducing actual harm.

Despite challenges in linking medication errors directly to patient harm, there is evidence of additional benefits from various interventions beyond a reduction in medication errors. For example, Myers and colleagues observed that the introduction of a computerized physician order entry (CPOE) system with clinical decision support (CDS) was also associated with a reduction in phone calls to pharmacy.[36] Similarly, Vardi and colleagues also demonstrated that this technology was associated with a reduction in the time taken

Table 4. Qualitative synthesis of reduction in medication errors identified in comparative studies according to intervention theme and type.

Intervention theme	Intervention type	Medication error type							
		Overall		Prescribing		Administration		Multiple	
		Median % error reduction (range)	n*	Median % error reduction (range)	n	Median % error reduction (range)	n	Median % error reduction (range)	n
Technology (n = 34)	Any	73 (−11–100)	33	85 (25–100)	18	52 (47–100)	5	58 (0–83)	9
	Barcoding	50 (47–52)	2	–	–	50 (47–52)	2	–	–
	CDS	77 (53–100)	2	77 (53–100)	2	–	–	–	–
	CPOE	66 (0–99)	5	96 (93–99)	2	47	1	33 (0–66)	2
	CPOE + CDS	78 (−11–100)	15	83 (25–100)	8	−11	1	62 (0–83)	6
	Computer programmes	96 (53–100)	6	94 (53–100)	5	100	1	–	–
	IV administration technology	73	1	–	–	73	1	–	–
Organizational (n = 14)	Any	50 (−16–100)	11	53 (48–100)	5	37 (−16–72)	5	39	1
	GPPs	51 (37–100)	6	59 (48–100)	4	37	1	39	1
	Medication distribution and supply	46 (−16–72)	4	–	–	46 (−16–72)	4	–	–
Personnel (n = 13)	Education	52 (14–87)	13	56 (14–86)	7	52 (14–87)	5	37	1
Hazard and risk analysis (n = 6)	Quality improvement tools	65 (59–74)	3	–	–	–	–	65 (59–74)	3
Pharmacy (n = 2)	Any	48 (17–79)	2	17	1	–	–	79	1
	Ward based	79	1	–	–	–	–	79	1
	Dispensary based	–	–	17	1	–	–	–	–
Multifactorial (n = 17)	Any	54 (15–100)	17	50 (15–76)	7	65 (63–67)	2	61 (17–100)	8
	GPPs + education	50 (24–76)	7	50 (44–76)	3	65 (63–67)	2	31 (24–37)	2
	GPPs + education + pharmacy	53 (15–100)	4	35 (15–54)	2	–	–	75 (51–100)	2
	GPPs + education + technology	70 (17–100)	5	46 (22–70)	2	–	–	71 (17–100)	3

CDS, clinical decision support; CPOE, computerized physician order entry; GPPs, guidelines, policies, and procedures; IV, intravenous.
*Does not add up to total number of comparative studies within each theme as not all studies reported an error risk difference.

to order resuscitation medications from 14.4 min to 2.1 min ($p < 0.001$).[44] Notably, Maat and colleagues identified no reduction in medication errors associated with their implementation of CDS to assist in managing hypo/hyperglycaemia, but they did observe reductions in time taken to perform simple (1.3; 0.3–2.3 min) or complex orders (8.6; 5.1–12.1 min).[49]

The potential for altered intervention effectiveness due to local variable factors is raised by Abboud and colleagues, who identified no reduction in gentamicin monitoring errors following the introduction of CDS as part of the prescribing process.[41] In this case, the authors suggested that the intervention had minimal benefit because they already had a clinical pharmacist responsible for ensuring monitoring was performed correctly, but results could differ in settings where clinical pharmacists are not present.

A common observation across studies that utilized a staged design to implement CPOE and then CDS was that maximal benefits were not gained until CDS was added.[46,48] Intuitively, this makes sense as CDS or computer programmes are usually developed to address activities that have already been predetermined to be high risk, and so have greater potential for reduction in medication errors. Notably, such improvements were not necessarily restricted to technology-based interventions. Less costly interventions involving paper-based prescribing and CDS, such as use of preprinted order forms, were identified as achieving similar reductions in medication errors to more expensive, computer-based approaches.[59,64] Therefore, in settings where CPOE systems are not readily available, lower-cost alternative approaches towards CDS are ideal.

An issue common across a number of studies was the need to adequately support staff in the implementation of any interventions, especially those that significantly change current practices. For example, with the introduction of automated infusion devices in drug libraries, there is a reliance on staff using the technology to its full extent in order to obtain maximal benefit. For various reasons, whether it be staff who consider the new process more complicated or too time consuming, work arounds may be created which can lead to medication errors. In introducing automated infusion devices, Manrique and colleagues monitored their use and identified an overall compliance rate of 78–85%.[21,22] While the automated infusion devices appeared extremely effective in preventing potentially catastrophic medication errors, compliance was still not ideal. Hennings and colleagues identified that neonatal ICU staff were almost twice as likely (RR 1.68; 1.18–2.38) to reprogramme pumps than adult ICU staff.[20] Whether this was just due to staff ignoring or overriding the alerts or because the medication library and associated functions were not sufficiently programmed for use in the neonatal unit is unclear. However, these examples highlight the importance around thorough implementation strategies and the requirement to constantly monitor and evaluate the use of new technologies as they are implemented within the neonatal unit. There is also the constant requisite to review and update such technologies as time goes on, as further advancements are made.

Strengths of our review include the comprehensive literature search strategy and inclusion of a broad range of comparative and noncomparative studies to explore the breadth of research previously undertaken on interventions for reducing medication errors in neonates. This is of particular usefulness in exploring the evaluation of different interventions to support implementation into clinical practice, as well as guide future research priorities.

Notwithstanding the comprehensive nature of our systematic review, several limitations bear consideration. First, significant variability was evident across all included studies, with differences in intervention strategies, trial methods, types of medication errors evaluated, and how medication errors were identified and evaluated. Such heterogeneity has been observed in previous systematic reviews of interventions to reduce paediatric medication errors.[12] A key aspect for overcoming limitations in the existing evidence base identified in this review lies in standardization of definitions and research methodologies for medication error studies. In particular, consistent grading of medication errors using universal reporting standards, such as the one endorsed by the National Coordinating Council for Medication Error Reporting and Prevention, would facilitate a greater understanding of the impact of interventions on harmful medication errors.[118] This is of importance as only eight of the identified studies reported separately on minor and major medication errors, demonstrating a significant difference in error reduction depending on the definition utilized. Notably, one of the studies identified a 16% increase in minor

medication errors following the introduction of the intervention, largely thought due to increased awareness and reporting of errors, but a substantial 100% reduction in major errors.[65] Others have also called for more consistent use of denominators that better reflect the total opportunities for error (e.g. prescribing errors per 1000 medication orders), rather than the use of other denominators such as medication errors per patient or per patient day;[12] the latter being considered more susceptible to bias from factors such as the criticality of the patient and number of medications being ordered, and limiting ability to accurately compare results across studies.

Conclusion

While neonatal medication errors can be reduced through multiple interventions aimed at improving the medication use process, no single intervention appeared superior. Despite the significant increase in the number of published studies focused on reducing neonatal medication errors, our knowledge of interventions to prevent neonatal medication errors remains hampered through a lack of uniformity in study design, data collection methodology, and outcome reporting. This heterogeneity leads to difficulties in developing clear guidance as to which interventions are best to adopt. Further research is required to evaluate the relative cost-effectiveness of the various medication safety interventions to facilitate decisions regarding uptake and implementation into clinical practice. Ultimately, the choice of the ideal interventions for improving medication safety will likely be an individual one, taking into consideration local resources, together with an understanding of the types and severity of errors that occur within the organization.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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