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REVIEW ARTICLE

Factors influencing in-hospital prescribing errors: A systematic review

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Aim: In-hospital prescribing errors (PEs) may result in patient harm, prolonged hospitalization and hospital (re)admission. These events are associated with pressure on healthcare services and significant healthcare costs. To develop targeted interventions to prevent or reduce in-hospital PEs, identification and understanding of facilitating and protective factors influencing in-hospital PEs in current daily practice is necessary, adopting a Safety-II perspective. The aim of this systematic review was to create an overview of all factors reported in the literature, both protective and facilitating, as influencing in-hospital PEs.

Methods: PubMed, EMBASE.com and the Cochrane Library (via Wiley) were searched, according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement, for studies that identified factors influencing in-hospital PEs. Both qualitative and quantitative study designs were included.

Results: Overall, 19 articles (6 qualitative and 13 quantitative studies) were included and 40 unique factors influencing in-hospital PEs were identified. These factors were categorized into five domains according to the Eindhoven classification ('organization-related', 'prescriber-related', 'prescription-related', 'technology-related' and 'unclassified') and visualized in an Ishikawa (Fishbone) diagram. Most of the identified factors (87.5%; $n = 40$) facilitated in-hospital PEs. The most frequently identified facilitating factor (39.6%; $n = 19$) was 'insufficient (drug) knowledge, prescribing skills and/or experience of prescribers'.

Conclusion: The findings of this review could be used to identify points of engagement for future intervention studies and help hospitals determine how to optimize prescribing. A multifaceted intervention, targeting multiple factors might help to circumvent the complex challenge of in-hospital PEs.

KEYWORDS
education, medication safety, prescribing errors, risk factors

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1 | INTRODUCTION

Prescribing errors (PEs) in the in-hospital setting may cause adverse drug events (ADEs),[1] resulting in patient harm, prolonged hospitalization or hospital readmission.[2–4] These events are associated with pressure on healthcare services and significant healthcare costs.[5] Over the years, several strategies have been implemented to reduce in-hospital PEs and associated patient harm. Examples of such strategies are the implementation of computerized physician order entry (CPOE) systems, often in combination with clinical decision support systems (CDSS), the addition of (clinical) pharmacists to medical teams,[6–9] and the introduction of medication reconciliation at hospital admission and discharge.[6,7,10,11] Although some of these interventions reduce PEs, medication-related harm caused by inappropriate medication and prescribing is not declining.[2,12,13] This underscores the need for more effective strategies to combat this problem.

The development of such strategies requires a thorough understanding of the complexity of in-hospital prescribing and the identification of factors that influence in-hospital PEs. We therefore searched the literature to identify and review all factors, both facilitating and protective, that have been identified as fully or partially influencing in-hospital PEs. A systematic review published in 2009 identified causes and factors facilitating in-hospital PEs, defined as either variables or reasons linked with the prevalence of (specific) PEs as reported by researchers or study subjects,[14] but did not look at protective factors, which is characteristic of a Safety-I approach.[15] To understand the complexity of daily in-hospital prescribing with the aim of reducing in-hospital PEs, factors that protect against in-hospital PEs should also be included, adopting a Safety-II perspective.[15] Since the review of 2009, the introduction of prescribing tools such as CPOE systems and CDSS[14] has probably influenced the prescribing process and the occurrence of PEs. For this reason, the aim of this systematic review was to create an updated overview of all factors, both facilitating and protective, reported in the literature as being associated with the occurrence of in-hospital PEs. A secondary aim was to analyse if and how the identified factors have changed over time.

2 | METHODS

2.1 | Data sources and study identification

The literature was searched in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.[16] To identify all relevant publications describing factors that were fully or partially responsible for, or associated with, in-hospital PEs, we developed a search strategy in collaboration with a medical information specialist (R.O.). The bibliographic databases PubMed, EMBASE.com and the Cochrane Library (via Wiley) were systematically searched from inception to 10 June 2020. Search terms included controlled terms (MeSH in PubMed and Emtree in Embase) as well as free-text terms in the Cochrane Library. Search terms expressing 'prescribing errors' were used in combination with search terms involving 'risk factors' and 'in-hospital setting'. The full search strategies for all databases can be found in Supporting information Table S1.

Duplicate articles were removed, and, during the first phase, two authors (R.M. and M.S.) independently screened all titles and abstracts. During the second phase, they independently assessed full texts for eligibility. In both phases, disagreements were resolved by consensus. If consensus was not reached, a third reviewer (M.R.) was consulted. Rayyan, a web and mobile app for systematic reviews, was used to streamline the screening process.[17]

2.2 | Study selection

Both qualitative (QL) and quantitative (QN) studies were included if they reported at least one factor, either facilitating or protective, as being either fully or partially responsible for, or associated with, in-hospital PEs in adult patients.[4] Prescriptions could be either handwritten or computerized. Patient-related factors were not investigated in this review because of the recent review of Saedder et al., who found that the number of drugs is the most frequently documented independent patient-related risk factor.[18] 'Factors' were defined based on the definition of Tully et al.[14] as: 'either variables, associations or reasons linked with the prevalence of (specific) prescribing errors as reported by researchers or study subjects'.

Studies published in English and Dutch were eligible for inclusion. Studies were not excluded based on their methodological quality in order to establish a complete overview of the in-hospital prescribing process resulting in PEs. However, the quality of the studies was assessed and reported as part of this systematic review. Studies involving specific medication group(s) or drugs (e.g., antiretroviral, antibiotics, onco-haematological agents and anticoagulants) or specific patient populations (e.g., the elderly, non-adult patients and patients with specific morbidities such as Alzheimer's disease, mental health disorders or diabetes) were excluded because findings may be population-specific and not generalizable or representative of the general in-hospital population. Likewise, studies performed in an intensive care unit (ICU) or emergency department (ED) were also excluded, except when patients were transferred to another ward and a distinction was made between the two wards. Articles without original data and non-peer reviewed documents (e.g., conference abstracts, case reports and presentations) were excluded.

If the full text of articles was not available, the catalogue of international medical centre libraries was accessed and corresponding authors were contacted personally by email. Articles that were still unavailable in full text thereafter were excluded. A detailed list of all inclusion and exclusion criteria is provided in Supporting information Table S2.

2.3 | Data extraction

In addition to the outcome measure, two authors (R.M. and M.S.) extracted the following data: year of publication, country in which the

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study results were obtained, period of data collection, study setting description including number of study sites and specification of clinical wards, study design and type (QL or QN), study subjects (number of patients, prescribers, prescriptions and PEs), type of prescribing procedure (handwritten, computerized or both) and authors' definition of a PE.

2.4 | Data analysis

All identified factors were categorized into five domains, in accordance with the Eindhoven Classification Model, an incident analysis tool for the medical field that classifies root causes of safety-related incidents,[19] as used in our previous study.[20] Subsequently, an Ishikawa (Fishbone) diagram was created to visualize the factors identified as influencing the in-hospital prescribing process resulting in PEs. Fishbone diagrams are used in root cause analyses to group, categorize and visualize multiple facilitators and protective barriers for an effect.[21]

Owing to the anticipated heterogeneity of eligible studies and the outcome measures reported, we did not perform a meta-analysis.

2.5 | Critical appraisal and inter-rater reliability

2.5.1 | Critical appraisal of QL studies

We used the consolidated criteria for reporting QL studies (COREQ)[22] to critically appraise the included QL studies. COREQ contains 32 items in three domains, namely, 'research team and reflexivity', 'study design' and 'analysis and findings'. Each item was scored as being reported according the COREQ description (scoring 1 point) or not (scoring 0 points), with a maximum score of 32.[23] Both the total score and summary score per domain were calculated for each QL study.

2.5.2 | Critical appraisal of QN studies

We used the Study Quality Assessment Tools of the National Institutes of Health National Heart, Lung, and Blood (NIH NHLB)[24] to critically appraise the included QN studies, based on the recommendations made by Ma et al.[25] The NIH NHLB Study Quality Assessment Tools contain six sub-tools. Each item was scored 'yes', 'no' or 'cannot determine/not reported/not applicable'. Per reviewer, an overall quality rating of each study was given as being 'good', 'fair' or 'poor'. One author (R.M.) and two external reviewers (M.W. for QL studies and J.A.D. for QN studies) performed this assessment independently.

2.5.3 | Inter-rater reliability

The unweighted kappa coefficient (κ) was calculated using SPSS 26 (IBM Corp., Armonk, NY) to test inter-rater reliability between both assessors of the QL and QN studies. Kappa coefficients were interpreted according to the scale of Landis and Koch.[26] Disagreements were resolved by consensus in order to obtain a final appraisal.

3 | RESULTS

3.1 | Search results

The search strategy yielded 8194 unique records after removal of duplicates. Through screening by title and abstract, 7949 articles were excluded as not meeting the inclusion criteria (Supporting information Table S2). Full-text assessment of the remaining 245 articles resulted in 226 articles not meeting the inclusion criteria or the full text could not be obtained despite previously mentioned additional efforts. A total of 19 articles[27–45] were included in this systematic review (Figure 1). The majority of studies (68.4%; $n = 13$) had a QN design (Supporting information Table S3).

3.2 | Study characteristics

Most studies were carried out in the United Kingdom ($n = 8$), Australia ($n = 5$) and the United States ($n = 2$). One study[29] did not report where the study was performed. Publication dates ranged from 1997 to 2019, but a majority of studies ($n = 3$) was published in 2008. A total of 12 studies (63.2%) were carried out at a single hospital, and all studies including more than one site were carried out in the same country (Supporting information Table S3).

3.3 | Critical appraisal and inter-assessor agreement

The total COREQ score of the included QL studies ranged from 11 to 20 out of 32 points. In general, the included QL studies scored relatively low on the first domain 'research team and reflexivity'. The highest score on this domain was 5[32] and the lowest was 0 points[45] out of a total of 8 points. However, the study that scored 0 points in the first domain scored the highest in the second domain 'study design' (10 out of 15 points). In general, all included QL studies scored relatively high on the third domain 'analysis and findings' with scores ranging from 4 to 8 points out of a total of 9 points. The unweighted kappa coefficient (κ) between both assessors of the QL studies (R.M. and M.W.) was $\kappa = 0.95$. The strength of agreement was considered as 'almost perfect'[26] based on $k = 2$ and $N = 192$. Full details of the final appraisal and the COREQ scores of the QL studies are provided in Supporting information Table S4.

Of the included QN studies, three (23.1%; $n = 13$) were appraised as 'poor'[36,37,42] and were observational studies. Three studies were assessed as 'good'[35,41,44] and the remaining eligible QN studies were assessed as 'fair'.[27,29,31,33,38–40] The unweighted kappa coefficient (κ) between assessors of the QN studies (R.M. and J.A.D.) was $\kappa = 0.60$.

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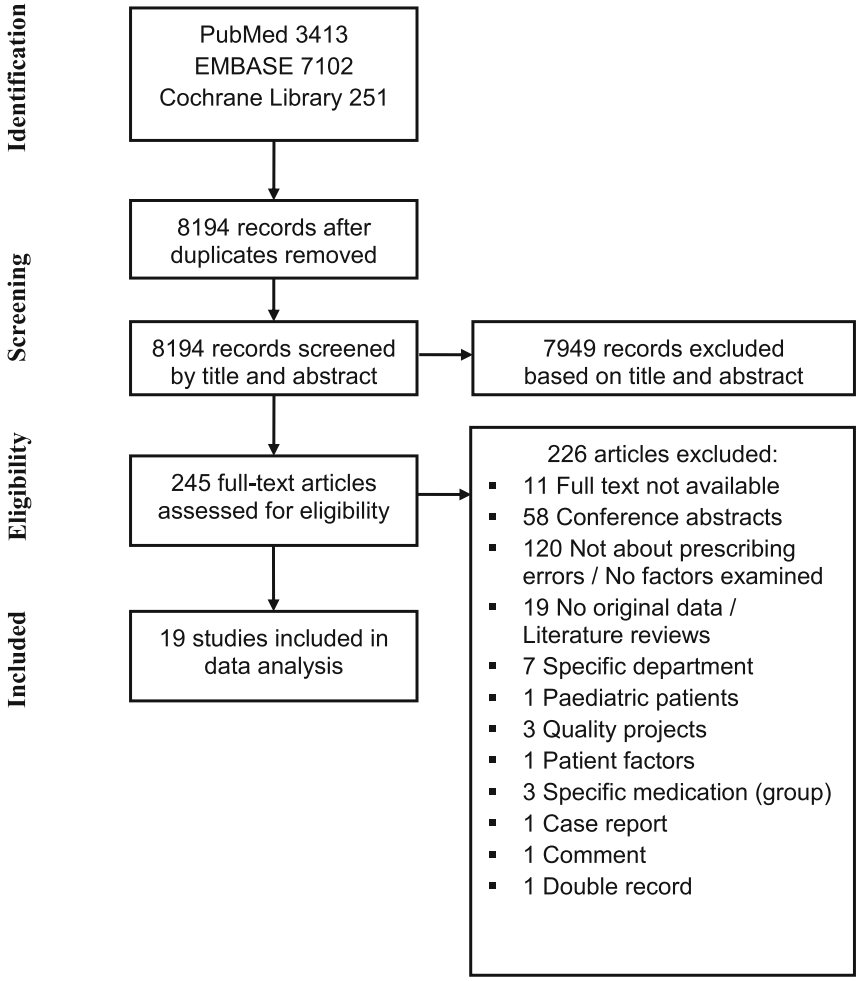

FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow diagram.

The strength of agreement was considered 'moderate'[26] based on $k = 3$ and $N = 174$. Full details of the appraisal of the QN studies are provided in Supporting information Table S4.

3.4 | Which factors influence in-hospital prescribing resulting in PEs?

In total, 40 unique factors were identified as influencing in-hospital PEs. These factors could be classified into the five domains of the Eindhoven Classification Model[19]: 'prescriber-related', 'prescription-related', 'technology-related', 'organization-related' and 'unclassifiable' factors (Table 1). An overview of identified factors is visualized in a Fishbone diagram (Figure 2). Most of the identified factors (87.5%) were classified as facilitating in-hospital PEs (Figure 2).

3.4.1 | Organization-related factors

Ten studies[28,29,31,32,34,36,39,41,43,45] identified 13 organization-related factors, of which two were considered as protective against in-hospital PEs (Figure 2). The facilitating factor identified most often (seven studies) was 'inadequate patient information', for example, because of missing relevant patient information and multiple, missing or hybrid medical charts.[28,29,31,32,34,36,45] 'Inadequate staffing and/or a high workload' was identified in five studies (26.3%)[28,32,34,39,45] and 'inadequate supervision' in four studies (21.1%)[28,32,34,45] as facilitating PEs. An example of inadequate supervision was no or insufficient feedback on prescribing, which left junior doctors unaware of their mistakes so that they kept repeating the same mistake.[45] These studies also identified constructive feedback, which was often provided by other healthcare providers, such as pharmacists, as protective against in-hospital PEs.

Other organization-related factors considered to facilitate in-hospital PEs were an 'inadequate physical workplace',[28,34,45] such as not having a desk or a cramped working place[28,34] or frequent distractions and interruptions during prescribing,[45] and 'no, inadequate or variable training for (new) prescribers'[36,39,45] on how to use computerized information and prescribing systems appropriately.

One (QN) study,[41] appraised as 'good', which used univariable and multivariable logistic regression models, found that medication orders issued at the time of hospital admission were more likely to be associated with a PE than those issued during the hospital stay (odds ratio [OR] 1.70; 95% confidence interval [CI] 1.61–1.80). This was

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TABLE 1 Study characteristics.

Domain	Adjusted factor influencing in-hospital prescribing errors (PEs)	Year	Author	Reference	Study type quantitative (QN) or qualitative (QL)	Critical appraisal[a]
Organization-related factors	Inadequate patient information (e.g., access, multiple hybrid [electronic and paper) or missing charts and unknown weight)	2002	Dean, B.	28	QL	17
		2002	Fijn, R.	29	QN	Fair
		2007	Hilmer, S	31	QN	Fair
		2008	Nichols, P.	32	QL	20
		2008	Coombes, I.D.	34	QL	19
		2011	Redwood, S.	36	QN	Poor
		2019	Puaar, S.J.	45	QL	18
	Inadequate staffing and/or a high workload	2002	Dean, B.	28	QL	17
		2008	Nichols, P.	32	QL	20
		2008	Coombes, I.D.	34	QL	19
		2013	Velez-Diaz-Pallares, M.	39	QN	Fair
		2019	Puaar, S.J.	45	QL	18
	Inadequate supervision (e.g., feedback on prescribing errors and culture)	2002	Dean, B.	28	QL	17
		2008	Nichols, P.	32	QL	20
		2008	Coombes, I.D.	34	QL	19
		2019	Puaar, S.J.	45	QL	18
	No, inadequate or variable training on information systems for (new) prescribers	2011	Redwood, S.	36	QN	Poor
		2013	Velez-Diaz-Pallares, M.	39	QN	Fair
		2019	Puaar, S.J.	45	QL	18
	Inadequate workplace (e.g., distractions and interruptions)	2002	Dean, B.	28	QL	17
		2008	Coombes, I.D.	34	QL	19
		2019	Puaar, S.J.	45	QL	18
	No or ambiguous guidelines and protocols	2002	Dean, B.	28	QL	17
		2008	Coombes, I.D.	34	QL	19
	Prescribing for an unfamiliar or unknown patient or beyond own expertise	2008	Nichols, P.	32	QL	20
		2008	Coombes, I.D.	34	QL	19
	Inadequate access to protocol, guidelines and/or drug information	2008	Nichols, P.	32	QL	20
	Prescribing of medication at hospital admission	2015	Ashcroft, D.	41	QN	Good
	Inadequate medication reconciliation at hospital admission	2002	Fijn, R.	29	QN	Fair
	Proactive surveillance and feedback on prescribing by other healthcare professionals (e.g., pharmacists and nurses)	2002	Dean, B.	28	QL	17
		2008	Coombes, I.D.	34	QL	19
		2018	Ferguson, J.	43	QL	11
	Prescribing of medication at hospital discharge	2015	Ashcroft, D.	41	QN	Good
Prescriber-related factors	Insufficient (drug) knowledge, prescribing skills and/or experience	2002	Dean, B.	28	QL	17
		2002	Fijn, R.	29	QN	Fair
		2005	Koppel, R.	30	QL	15
		2008	Nichols, P.	32	QL	20
		2008	Coombes, I.D.	34	QL	19
		2010	Abdel-Qader, D.	35	QN	Good

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TABLE 1 (Continued)

Domain	Adjusted factor influencing in-hospital prescribing errors (PEs)	Year	Author	Reference	Study type quantitative (QN) or qualitative (QL)	Critical appraisal[a]
		2013	Velez-Diaz-Pallares, M.	39	QN	Fair
		2015	Ashcroft, D.	41	QN	Good
		2019	Puaar, S.J.	45	QL	18
	Experiencing a high workload (e.g., busier than average and hectic)	2002	Dean, B.	28	QL	17
		2008	Nichols, P.	32	QL	20
		2008	Coombes, I.D.	34	QL	19
		2019	Puaar, S.J.	45	QL	18
	Impaired physical and/or mental well-being, resulting in failure of attention while prescribing (e.g., tiredness, hunger and stress)	2002	Dean, B.	28	QL	17
		2008	Nichols, P.	32	QL	20
		2008	Coombes, I.D.	34	QL	19
		2019	Puaar, S.J.	45	QL	18
	Relying on others (e.g., direct colleagues or pharmacists) to intercept errors	2002	Dean, B.	28	QL	17
		2008	Coombes, I.D.	34	QL	19
		2019	Puaar, S.J.	45	QL	18
	Indifferent attitude towards prescribing	2002	Dean, B.	28	QL	17
		2019	Puaar, S.J.	45	QL	18
	Inappropriate self-check on own prescribing	2019	Puaar, S.J.	45	QL	18
	Feeling pressured to prescribe medication	2008	Nichols, P.	32	QL	20
	Medical specialty	2002	Fijn, R.	29	QN	Fair
	Miscalculation	2008	Coombes, I.D.	34	QL	19
	Non-adherence to standardized procedures and/or guidelines	2013	Velez-Diaz-Pallares, M.	39	QN	Fair
	Relying on predefined medication order in CPOE	2019	Puaar, S.J.	45	QL	18
	Prescribing medication without observing patient first	2019	Puaar, S.J.	45	QL	18
	Self-check on own prescribing	2002	Dean, B.	28	QL	17
		2008	Coombes, I.D.	34	QL	19
	Medical specialty	2002	Fijn, R.	29	QN	Fair
Technique-related factors	Inadequate settings, technical failure or unnecessary complexity of CPOE	2005	Koppel, R.	30	QL	15
		2011	Redwood, S.	36	QN	Poor
		2013	Velez-Diaz-Pallares, M.	39	QN	Fair
		2013	Westbrook, J.	40	QN	Fair
		2019	Puaar, S.J.	45	QL	18
	Electronic prescribing facilitates new risks for and new types of PEs compared to paper-based prescribing.	2011	Redwood, S.	36	QN	Poor
	No or a lack of CDSS	2019	Puaar, S.J.	45	QL	18
	Alert fatigue	2019	Puaar, S.J.	45	QL	18
	Electronic prescribing results in a reduction of prescribing errors	2008	Donyai, P.	33	QN	Fair
		2013	Westbrook, J.	40	QN	Fair
		2015	Ashcroft, D.	41	QN	Good

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TABLE 1 (Continued)

Domain	Adjusted factor influencing in-hospital prescribing errors (PEs)	Year	Author	Reference	Study type quantitative (QN) or qualitative (QL)	Critical appraisal[a]
		2016	Núñez-Sánchez, A.	42	QN	Poor
		2018	Pontefract, S.	44	QN	Good
Prescription-related factors	The use of abbreviations	2012	Koffuor, G.A.	37	QN	Poor
		2012	Dooley, M.J.	38	QN	Fair
		2013	Velez-Diaz-Pallares, M.	39	QN	Fair
	Transcription of verbal orders	2002	Fijn, R.	29	QN	Fair
		2008	Coombes, I.D.	34	QL	19
		2013	Velez-Diaz-Pallares, M.	39	QN	Fair
	Illegible handwriting	1997	Winslow, E.	27	QN	Fair
		2012	Koffuor, G.A.	37	QN	Poor
	Specific dosage forms (e.g., eye preparations, inhalation devices and drugs with multiple oral forms)	2002	Fijn, R.	29	QN	Fair
		2010	Abdel-Qader, D.	35	QN	Good
	Incomplete prescriptions (missing information e.g., dosage and signature)	1997	Winslow, E.	27	QN	Fair
Other factors	Inadequate documentation in patient's medical record	2002	Dean, B.	28	QL	17
		2008	Nichols, P.	32	QL	20
		2008	Coombes, I.D.	34	QL	19
		2012	Koffuor, G.A.	37	QN	Poor
		2019	Puaar, S.J.	45	QL	18
	Interprofessional miscommunication	2002	Dean, B.	28	QL	17
		2008	Nichols, P.	32	QL	20
		2019	Puaar, S.J.	45	QL	18
	Miscommunication between healthcare professionals and patients (e.g., language difficulties and sedation)	2008	Coombes, I.D.	34	QL	19
	On Sunday an incident was more likely to occur than on Monday	2011	Redwood, S.	36	QN	Poor

Abbreviations: CDSS, computerized decision support system; CPOE, computerized order entry.
[a]Numbers correspond to COREQ scores.

considered a facilitating factor (Figure 2). The same study also found that medication orders issued at the time of hospital discharge were less likely to be associated with a PE than medication orders issued during the hospital stay (OR 0.77; 95% CI 0.72–0.82). This finding was therefore considered a protective barrier (Figure 2). No other studies identified either factor.

3.4.2 | Prescriber-related factors

A total of 14 prescriber-related factors were identified in nine studies[28–30,32,35,39,41,45,46] of which two were considered protective, namely, prescribers checking their own prescribing[28,34] and the medical specialty pulmonology.[29] The latter study also found, using univariable and multivariable logistic regression models, that the medical specialties of gynaecology and obstetrics and orthopaedics facilitated in-hospital PEs.[29] No explanation was provided for these findings. This study was appraised as 'fair'. None of the other included studies found specific medical specialties to influence in-hospital PEs.

'Insufficient drug knowledge, prescribing skills, and/or experience of the prescriber' was the main factor that facilitated PEs.[28–30,32,34,35,39,41,45] 'Impaired physical and/or mental well-being resulting in failure of attention while prescribing' was also associated with PEs.[28,32,34,45] Prescribers in these studies indicated that this factor was the result of being tired, stressed or hungry. Other facilitating factors were prescribers relying on others to intercept their PEs, for example, direct colleagues or pharmacists, and an indifferent attitude of prescribers towards prescribing,[28,45] for example, giving a low

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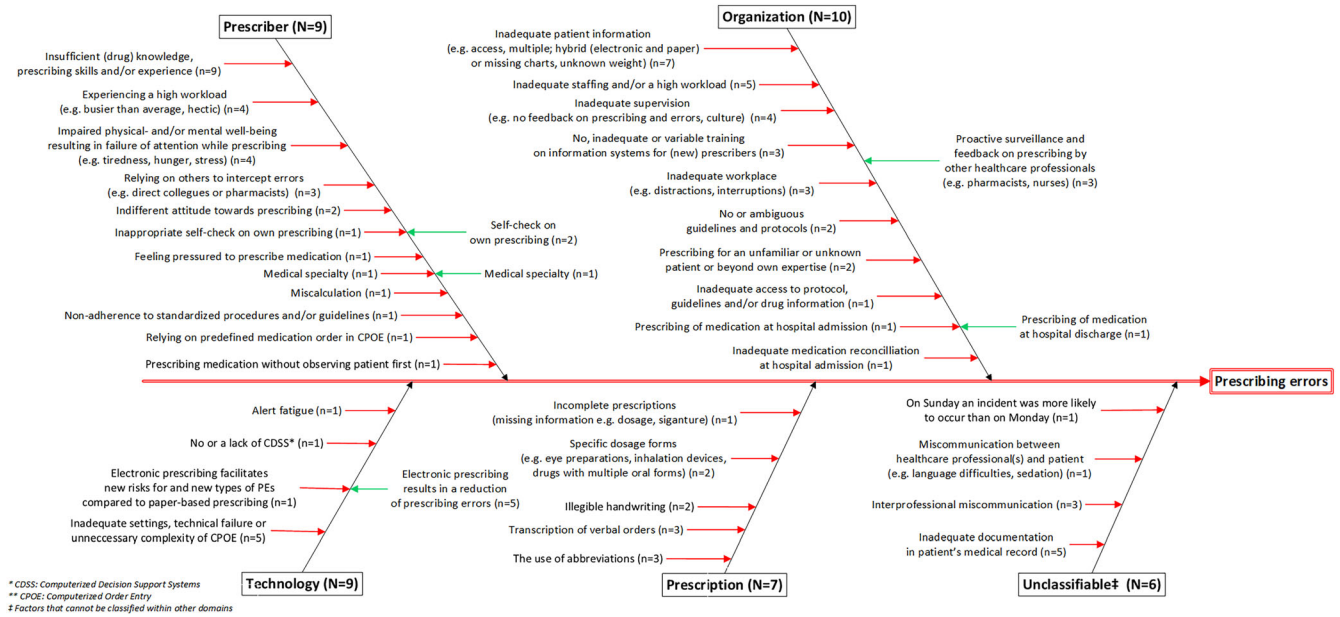

FIGURE 2 Fishbone diagram.

priority to prescribing[45] or not considering the task of prescribing important.[28] Within this domain, seven factors were identified in single studies[29,32,34,39,45] of which two were QN studies.[29,39]

3.4.3 | Technology-related factors

Five 'technology-related factors' were identified in nine studies.[30,33,36,39–42,44,45] Only one factor was considered to be protective, namely, 'electronic prescribing results in a reduction of PEs' (Figure 2), identified in five studies.[33,40–42,44] 'Inadequate settings, technical failure or unnecessary complexity of CPOE' was most often ($n = 5$) identified as facilitating PEs.[30,36,39,40,45]

While CPOEs are considered to reduce PEs,[33,40–42,44] they have technical weaknesses, such as being slow, being inadequately set up or raising too many non-tailored safety alerts, causing 'alert fatigue', so that helpful alerts for preventing PEs are ignored.[45] This shows that electronic prescribing facilitates new risks and types of PEs compared to paper-based prescribing.[36]

3.4.4 | Prescription-related factors

Five 'prescription-related factors' were identified in seven studies,[27,29,34,35,37–39] of which four studies concerned handwritten prescriptions.[27,29,34,37] All five factors facilitated in-hospital PEs.

The facilitating factor 'the use of abbreviations' was identified in three studies (15.8%)[37–39] and led to misinterpretation of prescriptions. This factor was applicable for both handwritten and computerized prescriptions. 'The use of abbreviations' became especially important in facilitating PEs during emergency situations, when instructions were given to nurses[39] or via telephone or pager to interns.[34] All three studies had a QN design, two of which were appraised as 'fair'[38,39] and one as 'poor'.[37] 'Transcription of verbal orders' to prescriptions was identified as facilitating PEs in three studies (15.8%).[29,34,39] Two of these studies had a QN design[29,39] and both were assessed as 'fair'. The QL study scored 19 out of 32 points on COREQ. The facilitators' 'illegible handwriting' and 'incomplete prescriptions due to missing information', e.g., dosage and signature, were only identified in studies that included handwritten prescriptions.[27,37] These studies had a QN design[27,37] of which one was appraised as 'fair'[27] and the other as 'poor'.

3.4.5 | Unclassifiable factors

Four factors were identified that could not be classified in other domains.[28,32,34,36,37,45] All were found to facilitate in-hospital PEs. The most frequently identified factor was 'inadequate documentation in patient's medical record', identified in five studies,[28,32,34,37,45] four of which were QL studies. The only QN study[37] within this domain was appraised as 'poor'. Incomplete or no documentation regarding why a specific drug was chosen or which drugs were currently prescribed appeared to result in PEs. Interprofessional miscommunication, both within a team and between teams,[28,32,45] was identified in QL studies only. 'Miscommunication between healthcare professionals and patients' due to language barriers or sedation was identified in one study,[34] and another study found that 'an incident was more likely to occur on Sunday than on Monday'.[36]

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4 | DISCUSSION

This systematic review of the literature yielded 19 eligible QL and QN studies that identified 40 unique factors that either facilitated or prevented in-hospital PEs. The identified factors were categorized into five domains, visualized in an Ishikawa (Fishbone) diagram. Most identified factors (87.5%) were considered as facilitating in-hospital PEs.

The presentation of factors that influence in-hospital PEs, using a Fishbone diagram, has, to our knowledge, not been done previously. The Fishbone diagram provides a schematic, visual presentation of study findings but can also be used to identify knowledge and evidence gaps in a field to be addressed in future research. For hospitals aiming to improve medication safety, this diagram can be used as a starting point to evaluate and improve the prescribing process in an in-hospital setting. Ideally, each in-hospital setting should identify which factors, both facilitating and protective, influence the occurrence of in-hospital PEs as they may differ between countries, hospitals and even clinical wards.[20] We therefore suggest that this Fishbone diagram be used as a starting point.

Several facilitating factors identified in our review are in line with those identified by Tully et al.[14] Examples are insufficient (drug) knowledge, prescribing skills and/or prescribing experience; impaired physical and/or mental well-being resulting in failure of attention while prescribing; inadequate staffing and/or a high workload; and inadequate physical workplace, such as not having a desk or a cramped working place or frequent distractions and interruptions during prescribing.

Only three of the 17 studies[28,29,34] included in the review by Tully et al. were eligible for inclusion in our review, because of the differences in inclusion and exclusion criteria. For example, Tully et al.[14] included ward-specific factors and factors identified in specific patient populations, such as ICU and paediatric patients. These findings are not generalizable or representative of the general in-hospital population, which was the focus of our study. In addition, and in contrast with Tully et al., we identified and included protective factors against in-hospital PEs in order to understand the complex process of daily in-hospital prescribing, adopting a Safety-II perspective. Unfortunately, we were able to identify only a few such factors in the literature. This might be because of a tendency to focus on what is going wrong in daily practice and how to improve the situation, representing the Safety-I perspective, instead of also reporting what is going right. With a Safety-II approach, more can be learned about the latter, for example, about the interplay of factors that facilitate or protect against in-hospital PEs ('work-as-done'), which better reflects daily practice.[47] Therefore, adopting a Safety-II approach might be an important topic for future research aimed at improving such a complex process as in-hospital prescribing.

An important question is which factors should be targeted in such multifaceted interventions to more effectively reduce in-hospital PEs. 'Organization-related factors' was the largest domain in this review, describing the setting and circumstances in which prescribers are expected to prescribe appropriately. Factors such as an inadequate workplace where prescribers are distracted or interrupted during prescribing,[28,34,45] inadequate patient information due to impaired CPOE access, multiple, hybrid (electronic and paper) or missing medical charts,[28,29,31,32,34,36,45] inadequate or variable training on information systems for (new) prescribers,[36,39,45] and a culture in which junior doctors do not feel able to question the decisions of seniors,[28] can negatively influence both the decision-making and writing processes underlying appropriate prescribing.[48,49] Structural commitment to improve these facilitating factors and situational awareness of in-hospital settings is needed. In line with a Safety-II approach[47] and to elucidate an intervention's effect and to enhance generalizability to other in-hospital settings, future intervention studies should report and include applicable organization-related factors, both facilitating or protecting against PEs, when reporting the effect of the intervention under investigation.

PEs can be defined as failures in the prescribing decision and writing processes.[49] The factor identified in most studies in our review was 'insufficient (drug) knowledge, prescribing skills, and/or prescribing experience'. This facilitating factor was identified in both QL and QN studies from 2002 to 2019, indicating that it is a persistent problem. Several interventions have targeted this facilitating factor, for example, having pharmacists participate on (high-risk) clinical wards.[6,7] Despite being effective, such 'corrective interventions' may circumvent the problems associated with insufficient (drug) knowledge and prescribing skills but do not address their underlying cause (e.g., inadequate education during medical training).

Several studies demonstrated that final-year medical students, that is, future prescribers, have insufficient clinical pharmacotherapeutic knowledge or prescribing skills and are inadequately prepared during their medical training to prescribe safely.[46,50–52] As junior doctors are responsible for most in-hospital prescriptions,[41,53] these alarming findings require protective, instead of corrective, interventions. An example of such a protective intervention is to incorporate pharmacology and prescribing education in an early phase of the medical curriculum, to improve the knowledge, prescribing skills and attitude towards prescribing of junior doctors and to provide a benchmark for a certain level of prescribing competence at graduation. Recent examples of such initiatives are the Prescribing Safety Assessment introduced in the United Kingdom,[54] the Dutch National Pharmacotherapy Assessment in the Netherlands,[55,56] and the European Prescribing Exam.[52] Post-academic education or introducing specific medical specialties to a ward team, such as pharmacists, could then be tailored to fill gaps in knowledge and skills encountered in daily practice.

The identification of technology- and prescription-related factors as potential facilitators of PEs highlights which failures can occur in the prescription writing process and how factors that influence in-hospital PEs have changed over time. Before the implementation of CPOEs, prescriptions were handwritten, and illegible handwriting and incorrect or missing information were found to increase the risk of PEs. Tully et al.[14] therefore hypothesized that the use of prescribing tools such as CPOEs would reduce the number of in-hospital PEs. Even though studies show a reduction in PEs with electronic prescribing, we found that these tools increased the risk of new and other

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types of in-hospital PEs. Although most hospitals require certification before prescribers can use a CPOE system, this general training seems insufficient to prevent inappropriate use and consequent PEs. These findings suggest that CPOE training should emphasize the potential for CPOE-related PEs and how to avoid them. Arguably, a certain baseline of prescribing knowledge must be assumed before such practical training can be effective. Even better would be to incorporate practical CPOE training in medical curricula, complementary to previously mentioned initiatives, to train future prescribers in safe prescribing. This can be effectuated by using the 'sandbox environment' of CPOEs, the mirrored production environment, mimicking the characteristics, functionalities and pitfalls of a CPOE but without affecting patients. These findings demonstrate the importance of continuous assessment of new tools assumed to reduce in-hospital PEs, in order to ensure their beneficial effect, for example, by using the Plan-Do-Check-Act (PDCA) cycle.[57]

Nevertheless, the findings of this review underscore that in-hospital prescribing is a complex process, influenced by multiple, human and non-human, factors. This emphasizes that a multifaceted approach might be more effective in reducing in-hospital PEs. We therefore suggest that a multidisciplinary, in-hospital team consisting of experts in the in-hospital prescribing process should provide pharmacotherapeutic stewardship and address factors that facilitate in-hospital PEs and reinforcing protective barriers against in-hospital PEs.

4.1 | Limitations

Our systematic review has some limitations. First, either some factors were identified in only one study, as shown in the Fishbone diagram and Table 1, or the quality of studies was appraised as 'poor', or both. The findings of these studies should be interpreted with caution and should be verified in future studies. Future research should focus on the extent to which only qualitatively identified factors are also statistically significant predictors. Another limitation is the diversity of definitions used for PEs in the studies included in this review. This makes it difficult to compare factors identified as influencing in-hospital PEs. In future studies, researchers should provide a definition of what constitutes a PE in their study and preferably use an established definition.[58] Lastly, most of the factors identified in this review came from studies performed in economically developed countries, so that potentially relevant factors may have been missed in other, less economically developed, countries. Nonetheless, the identified factors and Fishbone diagram can help future researchers identify points of engagement for new intervention studies and help organizations determine whether the factors identified in the Fishbone diagram influence prescribing and PEs in their hospital and how to optimize prescribing.

4.2 | Strengths

First, identifying and reporting protective and facilitating factors from both QN and QL studies with different study designs provides as complete an overview as possible of the complex process of daily in-hospital prescribing resulting in PEs. These findings can be used to develop more effective, multifaceted interventions to mitigate in-hospital PEs and to determine which factors should be investigated further in future research, for example, because they were identified in only one study, by a 'poor' quality study or only in QL studies. Secondly, by reviewing the literature from database inception, we were able to study the evolution of certain factors over time. This is important because some factors influencing in-hospital PEs seem to emerge, merge and disappear over time depending on the availability of new tools, such as CPOEs and CDSSs. This was particularly apparent for the domains of 'prescription-related' and 'technology-related factors'. This makes the findings of this review inclusive and applicable to countries where these relatively new tools are not the standard of care and prescriptions are handwritten. Lastly, because assessing factors that influence the occurrence of PEs in settings requires time and resources, the results of this systematic review, visualized in a Fishbone diagram, can be used as a starting point to evaluate and improve the prescribing process in an in-hospital setting to develop targeted interventions.

5 | CONCLUSION

Multiple factors influence the occurrence of in-hospital PEs emphasizing the need for a multifaceted approach, which addressed factors that facilitate PEs while also strengthening existing preventive factors. We suggest a multidisciplinary, in-hospital team should provide pharmacotherapeutic stewardship to meet this need. Future intervention studies should report which facilitating factors are targeted by their intervention and which protective factors are already present in the in-hospital setting, in order to better estimate an intervention's effect.

The findings of this review could be used to identify points of engagement for future intervention studies and help settings determine how to optimize in-hospital prescribing to reduce and prevent in-hospital PEs.

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COMPETING INTERESTS

The authors declare no conflict of interest.

CONTRIBUTORS

Mahomedradja, Sigaloff, Tichelaar and Agtmael were responsible for the conception or design of the work. Mahomedradja, Schinkel and Otten acquired the data. Mahomedradja, Schinkel, Reumerman,

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Sigaloff, Tichelaar, and Agtmael were responsible for the analysis and interpretation of the data. All the authors took part in the drafting of manuscript and gave it their final approval. All the authors agree to be accountable for all aspects of the work.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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