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ORIGINAL ARTICLE

Prevalence and determinants of medication administration errors in clinical wards: A two-centre prospective observational study

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Abstract

Aims and objectives: To identify the prevalence and determinants of medication administration errors (MAEs).

Background: Insight into determinants of MAEs is necessary to identify interventions to prevent MAEs.

Design: A prospective observational study in two Dutch hospitals, a university and teaching hospital.

Methods: Data were collected by observation. The primary outcome was the proportion of administrations with one or more MAEs. Secondary outcomes were the type, severity and determinants of MAEs. Multivariable mixed-effects logistic regression analyses were used for determinant analysis. Reporting adheres to the STROBE guideline.

Results: MAEs occurred in 352 of 2576 medication administrations (13.7%). Of all MAEs (n = 380), the most prevalent types were omission (n = 87) and wrong medication handling (n = 75). Forty-five MAEs (11.8%) were potentially harmful. The pharmaceutical forms oral liquid (odds ratio [OR] 3.22, 95% confidence interval [CI] 1.43–7.25), infusion (OR 1.73, CI 1.02–2.94), injection (OR 3.52, CI 2.00–6.21), ointment (OR 10.78, CI 2.10–55.26), suppository/enema (OR 6.39, CI 1.13–36.03) and miscellaneous (OR 6.17, CI 1.90–20.04) were more prone to MAEs compared to oral solid. MAEs were more likely to occur when medication was administered between 10 a.m.–2 p.m. (OR 1.91, CI 1.06–3.46) and 6 p.m.–7 a.m. (OR 1.88, CI 1.00–3.52) compared to 7 a.m.–10 a.m. and when administered by staff with higher professional education compared to staff with secondary vocational education (OR 1.68, CI 1.03–2.74). MAEs were less likely to occur in the teaching hospital (OR 0.17, CI 0.08–0.33).

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Day of the week, patient-to-nurse ratio, interruptions and other nurse characteristics (degree, experience, employment type) were not associated with MAEs.

Conclusions: This study identified a high MAE prevalence. Identified determinants suggest that focusing interventions on complex pharmaceutical forms and error-prone administration times may contribute to MAE reduction.

Relevance to clinical practice: The findings of this study can be used to develop targeted interventions to improve patient safety.

KEYWORDS
administration, medication errors, medication systems, patient safety, risk factors

1 | INTRODUCTION

Unsafe medication practices are a leading cause of patient harm globally (Panagioti et al., 2019; World Health Organization, 2017). Especially the administration of medication to patients is a critical step because an error at this stage may directly harm a patient and may have great impact on the staff member involved. The medication administration process is prone to errors due to its multistep nature. Contributing factors also include the multiplicity of services and people involved, complexity of procedures, and the frequent introduction of new procedures and technologies. The responsibility for administering medication to hospitalised patients is allocated to nurses, which have a multitude of other complex tasks related to direct patient care. In the last decades, many hospitals worldwide, including Dutch hospitals, have implemented several interventions such as computerised physician order entry (CPOE) and electronic medication administration record (eMAR) to support nursing staff in their daily routine and to reduce the number of medication administration errors (MAEs) (Keers et al., 2014; Manias et al., 2020; Westbrook et al., 2020). Still, the continuously high MAE rates (Kuitunen et al., 2021b; Manias et al., 2020; Westbrook et al., 2020) warrant additional supportive and preventive measures. Identifying determinants associated with MAEs in these settings is crucial, as they may form the basis for targeted interventions.

What does this paper contribute to the wider global clinical community?

- Medication administrations errors, including harmful errors, are prevalent in hospital settings, even with systems such as electronic medical record, computerised physician order entry and electronic medication administration record in place.
- Rates of medication administration errors differed between hospitals, which suggest that organisational factors, including different patient populations, are contributing factors.
- Medication administration errors were more likely to occur with complex pharmaceutical forms as well as between 10 a.m.–2 p.m. and 6 p.m.–7 a.m.
- These determinants could be the focus of targeted interventions to tackle medication administration errors and therefore to improve patient safety in hospitals.

2 | BACKGROUND

Medication errors occur frequently in healthcare settings and may lead to increased patient morbidity, mortality and healthcare costs (Batel Marques et al., 2016; Berdot et al., 2013; Keers et al., 2013b; Panagioti et al., 2019). The medication administration process is susceptible to many types of errors, such as omission and wrong dose. Systematic reviews examining the prevalence of MAEs or the effectiveness of strategies to reduce the occurrence of MAEs report substantial rates of MAEs (Berdot et al., 2013; Keers et al., 2013b; Kuitunen et al., 2021b; Manias et al., 2020). One systematic review reports a median error rate of 8.0% (interquartile range [IQR] 5.1%–10.9%) excluding wrong time errors (WTEs), while another reports a median error rate of 10.5% (IQR 7.3%–21.7%) (Berdot et al., 2013; Keers et al., 2013b).

Several strategies have been examined to prevent MAEs, such as electronic medical record (EMR), CPOE and eMAR systems; simulation-based training; and barcode-assisted medication administration (Berdot et al., 2016; Hutton et al., 2021; Keers et al., 2014; Kuitunen et al., 2021b; Manias et al., 2020; Shah et al., 2016). Many of these interventions are costly and target only a few MAE types. In addition, technological issues and human factors (e.g. workarounds) can compromise the effectiveness of these interventions (Mulac et al., 2021; van der Veen et al., 2018).

Reviews based on qualitative and quantitative studies report many potential causes of MAEs related to knowledge (e.g. lack of medication knowledge), personal circumstances (e.g. fatigue and complacency) and environmental context (e.g. interruptions, heavy workload and equipment design) (Keers et al., 2013a, 2015; Kuitunen et al., 2021a; Parry et al., 2015; Schroers et al., 2020). However, quantitative studies show conflicting results with regard to associated determinants (e.g. day of the week, time of administration or nursing staff characteristics), which may be explained by the clinical and methodological heterogeneity of these studies in terms of setting, country, use of technology and data collection methods

(Alemu et al., 2017; Baraki et al., 2018; Berdot et al., 2012; Blignaut et al., 2017; Feleke et al., 2015; Hammoudi et al., 2018; Harkanen et al., 2015; Nguyen et al., 2015; Ong & Subasyini, 2013; Prot et al., 2005; Rodriguez-Gonzalez et al., 2012; Sears & Goodman, 2012; Tissot et al., 2003; van den Bemt et al., 2002; Wondmieneh et al., 2020). Many of these studies focused on specific clinical ward types such as paediatric and intensive care units. Moreover, several older studies or studies in developing countries do not reflect modern clinical practice. Many hospitals, mostly in middle-income and high-income countries, have meanwhile implemented quite effective preventive strategies, including EMR, CPOE and eMAR. Studies on the determinants of MAEs in modern clinical practice—that is with supportive electronic medication systems—are scarce. Moreover, to our knowledge, a study of this kind has not yet been performed in a setting with an EMR, a CPOE and an eMAR system in place. Seeing that MAEs are still prevalent in modern hospitals with these systems, it is important to identify targeted interventions to minimise the number of these errors in such hospitals. Hence, we conducted a prospective observational study to identify the prevalence, type and potential severity of MAEs, as well as determinants of MAEs in two Dutch hospitals that have several supportive electronic medication systems (i.e. EMR, CPOE and eMAR) in place.

3 | METHODS

This study was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies (Appendix S1).

3.1 | Study design

This prospective observational study was performed in Erasmus MC, University Medical Center Rotterdam in Rotterdam, the Netherlands and in Amphia Hospital in Breda, the Netherlands, respectively, a university hospital and general teaching hospital. The Medical Ethics Review Committee of Erasmus MC waived approval for this study (reference number MEC-2018-1532) in accordance with the Dutch Medical Research involving human subjects Act. Verbal consent from nursing staff members was obtained for participation in this study, and data were handled confidentially according to the Dutch General Data Protection Regulation.

3.2 | Study setting

Data collection took place from October 2018 through February 2019 in Erasmus MC and from June 2019 through August 2019 in Amphia Hospital. Both hospitals had an EMR, a CPOE system and an eMAR system in place. This study was performed several months before planned extensive operations to improve medication safety, such as barcode-assisted medication administration. Table 1 shows the setting characteristics.

3.3 | Definitions and classification of MAE

In our study, an MAE was defined as any error during the administration of medication by nursing staff, that is a deviation from medication orders used by the nursing staff to administer medication, a deviation from local medication administration protocols, or a deviation from the medication information sheets provided by the manufacturer if local protocols were not available. Procedural errors (e.g. hygiene errors and labelling errors) and WTEs were not within the scope of this study. WTEs were excluded because they are highly prevalent (Berdot et al., 2013; Keers et al., 2013b) and generally considered as minor errors by clinicians. MAEs were classified into the following categories (Allan & Barker, 1990; van den Bemt & Egberts, 2007): omission, wrong medication handling, wrong dose, wrong administration technique, unordered drug, wrong dosage form, wrong route of administration, expired medication and other. Regarding the category wrong dose, deviations of more than 10% of the declared dose were marked as an MAE, considering that a deviation of 10% or less for the declared dose of pharmaceutical products within the shelf-life is widely accepted (International Conference on Harmonisation, 1999). The potential severity of MAEs was categorised according to the National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) severity index, which ranges from category A (circumstances or events that have the capacity to cause error) to I (an error occurred that may have contributed to or resulted in the patient's death) (National Coordinating Council for Medication Error Reporting & Prevention, 2001).

3.4 | Data collection

We collected data on medication administration using the disguised observation method (Allan & Barker, 1990; Dean & Barber, 2001), meaning that nursing staff were not aware of the detailed purpose of the study to prevent a Hawthorne effect. They were informed that the study was performed to examine the medication process. Observers that had completed an extensive training programme of several days accompanied the nursing staff to observe and record every dose administration on data collection forms designed for this study. After having arrived at a ward, observers selected the nurses to be observed through convenience sampling. Observation rounds were planned in periods of 1–2 weeks for each clinical ward. For ethical reasons, observers were instructed to intervene right before the administration if they had noticed a severe MAE (i.e. a dose deviation of at least 20%, wrong patient or wrong medication). Observation data were compared with medication prescriptions and protocols after the observation and not during observation, which complies with the gold standard of methods to detect medication errors (Dean & Barber, 2001). For each hospital, two raters independently

TABLE 1 Setting characteristics

Characteristics	Erasmus MC, University Medical Center Rotterdam	Amphia Hospital
Hospital characteristics		
Hospital type	University hospital	Teaching hospital
Clinical wards	Internal oncology	Internal medicine
	Neurology	Neurology
	Pulmonary medicine	General surgery
	Haematology	Orthopaedic surgery one
	Neurosurgery	Orthopaedic surgery two
	Hepatopancreatobiliary surgery	
System features		
EMR, eMAR, CPOE software[a]	HiX®	Epic®
Additional CPOE[a]	Practocol®	Not applicable
BCMA	No	For parenteral medication
Patient identification verification by scanning	Yes	Yes
Medication cart filling	Decentrally and manually by nursing staff in the clinical wards	Decentrally and manually by pharmacy staff in the clinical wards
Instructions on medication administration	Electronic protocols for oral and parenteral medication	Electronic protocols for oral and parenteral medication

Abbreviations: BCMA, barcode-assisted medication administration; CPOE, computerised physician order entry; eMAR, electronic medication administration record; EMR, electronic medical record.

[a]HiX® version 6.1 (ChipSoft B.V.; Amsterdam, the Netherlands); Epic® (Epic Systems Corporation; Verona, Wisconsin, United States); Practocol® version 2.0.9.3 and 2.1.5.1 (Practocol B.V.; Rotterdam, the Netherlands). Practocol® is the system for prescriptions of medication in chemotherapy protocols.

reviewed approximately 200 observations (n = 405 observations, i.e. 405 medication administrations, in total over the two hospitals) to assess the presence, type and severity of MAEs, and disagreement was resolved by consensus between the two raters. The raters were one pharmacist (JJ) and hospital pharmacist (NH) in Erasmus MC and one hospital pharmacy resident (MR) and pharmacy student in Amphia Hospital. After exclusion of 2 of the 405 observations because of missing reviewer data, the Cohen's kappa for the presence of one or more MAEs was 0.81, indicating high interrater reliability. Therefore, the remaining observations were reviewed by one reviewer (JJ or MR) to assess whether an MAE occurred. Subsequently, the type and severity of each MAE were assessed by JJ and NH in Erasmus MC and MR and one pharmacist in Amphia Hospital and disagreement between the two raters was resolved by consensus.

After completion of the observation period in a particular clinical ward, data on staff member characteristics were collected on forms by e-mail or in person. JJ or MR categorised the medication class by Anatomical Therapeutic Chemical class (WHO Collaborating Centre for Drug Statistics Methodology, 2020) and the day of the week of each observed medication administration. In Erasmus MC, patient-characteristic data (i.e. gender, birth date and number of prescribed medications per day) were collected by JJ from the EMR system HiX® (Chipsoft B.V.; Amsterdam, the Netherlands) and from the CPOE system Practocol® (Practocol B.V.; Rotterdam, the Netherlands) for medication in chemotherapy protocols. In Amphia Hospital, patient-characteristic data were collected by MR from the EMR system Epic® (Epic Systems Corporation; Verona, Wisconsin, United States). Collected data were processed in OpenClinica® version 2.1 (OpenClinica LLC; Waltham, Massachusetts, United States).

3.5 | Inclusion and exclusion criteria

Medication administrations to inpatients performed by nursing staff were included. Excluded were medication administrations that were 1. not completed during the observation, 2. were declined by patients for other reasons than being erroneous, or 3. medication administrations with the medication name missing on the data collection form.

3.6 | Study outcomes

The primary outcome was the proportion of medication administrations with one or more MAEs. The secondary outcomes were the type and potential severity of MAEs and the association between determinants and the occurrence of one or more MAEs.

We considered the following potential determinants: pharmaceutical form; medication class; hospital type; clinical ward type; day of the week; time window; patient-to-nurse ratio (i.e. number of

patients per nurse); interruptions; double check of parenteral medication administration; and nursing staff age, gender, educational level, degree type and employment type. Considered determinants were based on proposed associations in literature and on theoretical assumptions (Alemu et al., 2017; Baraki et al., 2018; Berdot et al., 2012; Feleke et al., 2015; Hammoudi et al., 2018; Harkanen et al., 2015; Keers et al., 2013a; Keers et al.; 2015; Kuitunen et al., 2021a; Nguyen et al., 2015; Ong & Subasyini, 2013; Parry et al., 2015; Prot et al., 2005; Rodriguez-Gonzalez et al., 2012; Sears & Goodman, 2012; Tissot et al., 2003; van den Bemt et al., 2002; Wondmieneh et al., 2020).

3.7 | Sample size calculation

Assuming an MAE rate of 10% (Berdot et al., 2013; Hassink et al., 2012; Keers et al., 2013b; Shah et al., 2016), a sample size of at least 1700 administrations would be required to examine 17 variables, using the rule of thumb that only one variable should be studied for every ten events (Peduzzi et al., 1996). The aim was to include at least 2000 administrations because the number of repeated measurements on nurse and patient level could not be predicted with convenience sampling. A total of 136 observation rounds were planned in advance (based on the expected number of observations per round), distributed over different days of the week and time windows. An extension was not needed, but the number of rounds was planned to be extended if fewer than 2000 administrations were included.

3.8 | Data analysis

Descriptive statistics were used for the prevalence, type and severity of MAEs. Both univariable and multivariable mixed-effects logistic regression analyses (i.e. generalised linear mixed models) were used to determine the association between the determinants and MAEs accounting for within-subject correlations due to repeated measurements within the nurse and patient level.

Because of data clustering and the quantified number of MAEs in our study, fewer variables were tested than planned. The following variables were examined in the mixed-effects logistic regression analyses: pharmaceutical form (categorised; oral solid, oral liquid, infusion, injection, nebulising solution, ointment, suppository/enema, miscellaneous); hospital type (categorised; university hospital, teaching hospital); day of the week (categorised; weekdays, weekend); time window (categorised; 7 a.m.–10 a.m., 10 a.m.–2 p.m., 2 p.m.–6 p.m., 6 p.m.–7 a.m.); patient-to-nurse ratio (continuous); interruptions during administration (categorised: yes, no); and nursing degree type (categorised; nurse, specialised nurse, other), educational level (categorised; secondary vocational education, higher professional education, other), employment type (categorised; temporary, non-temporary), and experience in healthcare settings (categorised; 0–1 year, 1–5 years, more than 5 years). Medication class was excluded from the analysis because of the high number of classes in addition to assumed limited added value. The variable hospital type was chosen instead of clinical ward type because of low power for including the latter in the analysis. Because of the low number of participating male nursing staff members (n = 8, 6.1%), gender was excluded. Nurses' age and experience since first nursing diploma registration were excluded because of multicollinearity with experience in healthcare settings.

Two main multivariable mixed-effects logistic regression analyses were performed, with and without nursing staff characteristics, because staff characteristic data were only available for 55.7% of observed nurses. For the univariable model and the multivariable model without staff characteristics, two random effects, that is a random intercept by staff member and a random intercept by patient, were included to account for repeated measurements and the within-subject correlations. For the multivariable model with staff characteristics, only a random effect by patient was included, because a random intercept by staff member had no significant effect in the model.

The variable 'double check of parenteral medication administration' was excluded from the main analysis because only a limited portion of our data concerned parenteral medication. We performed post hoc analyses for this variable, that is a univariable and multivariable mixed-effects logistic regression analysis, which included two random intercepts (by staff member and patient) and the following confounders that were categorised identically to the main model: hospital type, day of the week, time window and patient-to-nurse ratio. For all logistic regression models, complete case analyses were performed. Odds ratios with 95% confidence intervals are presented. Data analyses were performed with R Statistics® version 4.0.2. (The R Foundation; Vienna, Austria) for the mixed-effects logistic regression analyses and with SPSS Statistics® version 25 (IBM Corporation, Armonk, New York, United States) for other analyses.

4 | RESULTS

A total of 2629 medication administrations administered by 235 nursing staff members to 416 patients were observed. A total of 53 observations (2.0%), particularly oral solids (n = 46), were excluded from MAE analyses because patients declined administration for other reasons than being erroneous. Observers intervened in nine administrations. The characteristics of the included 2576 medication administrations, nursing staff members and patients are shown in Table 2.

4.1 | Prevalence, type and severity of MAEs

The prevalence, type and severity of MAEs are shown in Table 3. Of the 2576 included medication administrations, one or more MAEs occurred in 352 administrations (13.7%). Of the total number of MAEs (n = 380), the most common MAE types were omissions (n = 87,

TABLE 2 Characteristics of observed medication administrations, nursing staff members and patients

Characteristics	
Observed medication administrations, *n*	2576
Medication characteristics	
Pharmaceutical form[a], *n* (%)	
Oral solid	1800 (69.9)
Oral liquid	92 (3.6)
Infusion	273 (10.6)
Injection	241 (9.4)
Nebulising solution	72 (2.8)
Ointment	30 (1.2)
Suppository/enema	19 (0.7)
Miscellaneous	48 (1.9)
Medication class (ATC code), *n* (%)	
Alimentary tract and metabolism (A)	612 (23.8)
Blood and blood forming organs (B)	230 (8.9)
Cardiovascular system (C)	226 (8.8)
Dermatologicals (D)	28 (1.1)
Genitourinary system and sex hormones (G)	13 (0.5)
Systemic hormonal preparations (H)	93 (3.6)
Anti-infectives for systemic use (J)	286 (11.1)
Antineoplastic and immunomodulating agents (L)	64 (2.5)
Musculoskeletal system (M)	46 (1.8)
Nervous system (N)	823 (31.9)
Antiparasitic products (P)	1 (0.0)
Respiratory system (R)	117 (4.5)
Sensory organs (S)	20 (0.8)
Other (V)	17 (0.7)
Ward characteristics	
Clinical ward, *n* (%)	
University hospital	
Internal oncology	252 (9.8)
Neurology	196 (7.6)
Pulmonary medicine	375 (14.6)
Haematology	234 (9.1)
Neurosurgery	281 (10.9)
Hepatopancreatobiliary surgery	152 (5.9)
Teaching hospital	
Internal Medicine	265 (10.3)
Neurology	236 (9.2)
General surgery	221 (8.6)
Orthopaedic surgery one	190 (7.4)
Orthopaedic surgery two	174 (6.8)
Time characteristics	
Day of the week, *n* (%)	
Monday	437 (17.0)
Tuesday	386 (15.0)
Wednesday	511 (19.8)
Thursday	471 (18.3)
Friday	266 (10.3)
Saturday	231 (9.0)
Sunday	274 (10.6)
Time window, *n* (%)	
7 a.m.–10 a.m.	961 (37.3)
10 a.m.–2 p.m.	408 (15.8)
2 p.m.–6 p.m.	551 (21.4)
6 p.m.–7 a.m.	656 (25.5)
Workload characteristics	
Patient-to-nurse ratio[b], median (IQR)	6 (4–8)
Interruptions[c], *n* (%)	
Yes	262 (10.2)
Staff characteristics	
Observed staff members[d], n	235
Staff members, personal data available, *n* (%)	131 (55.7)
Male, *n* (%)	8 (6.1)
Age, median (IQR)	28 (24–47)
Nursing degree type, *n* (%)	
Nurse	91 (69.5)
Specialised nurse	28 (21.4)
Student nurse	10 (7.6)
Other	2 (1.5)
Educational level[e], *n* (%)	
Secondary vocational education	56 (43.1)
Higher professional education	62 (47.7)
University education	2 (1.5)
Other	10 (7.7)
Experience since nursing diploma, *n* (%)	
0–1 year	20 (15.3)
1–5 years	33 (25.2)
More than 5 years	67 (51.1)
Not applicable	11 (8.4)
Experience in healthcare settings[e], *n* (%)	
0–1 year	1 (0.8)
1–5 years	43 (33.1)
More than 5 years	86 (66.2)
Employment type[e], *n* (%)	
Non-temporary	117 (90.0)
Temporary	7 (5.4)
Other	6 (4.6)
Patient characteristics	
Patients, *n*	416
Male, *n* (%)	214 (51.4)

(Continues)

TABLE 2 (Continued)

Characteristics	
Age, median (IQR)	65 (54–74)
Prescribed medications per day, median (IQR)	13 (9–16)

Abbreviations: ATC, Anatomical Therapeutic Chemical; IQR, interquartile range.

[a]Missing, $n = 1$. Miscellaneous: eye drops, eye gel, inhalation aerosol or powder, intestinal gel, nasal spray, patch.

[b]Missing, $n = 61$.

[c]Missing, $n = 9$.

[d]Range of observed staff members in each clinical ward: university hospital 22–38, teaching hospital 7–16.

[e]Missing, $n = 1$.

22.9%), wrong medication handling ($n = 75$, 19.7%) and wrong dose ($n = 73$, 19.2%). Of all errors, 45 (11.8%) were potentially harmful MAEs, that is errors classified in NCC MERP category E or higher. Examples of potentially harmful MAEs are shown in Appendix S2.

4.2 | Determinants of MAEs

The associations between the potential determinants and MAEs are shown in Table 4. Compared to oral solids, the following forms were more prone to MAEs: oral liquid, infusion, injection, ointment, suppository/enema and miscellaneous (eye drops, eye gel, inhalation aerosol or powder, intestinal gel, nasal spray, patch). MAEs were more likely to occur between 10 a.m.–2 p.m. and 6 p.m.–7 a.m. compared to 7 a.m.–10 a.m. Furthermore, MAEs were more likely in the university hospital compared to the teaching hospital or when nursing staff with higher professional education administered medication compared to nursing staff with secondary vocational education. Associations were comparable in the multivariable analysis without staff characteristics, except for the time window 6 p.m.–7 a.m. In the multivariable analyses, no significant associations were found for the determinants day of the week, patient-to-nurse ratio, interruptions and staff characteristics other than educational level.

4.3 | Association between double checking of parenteral medication administration and MAEs

Parenteral medication administrations accounted for 24.8% ($n = 248$) of administrations in the university hospital and for 11.4% ($n = 126$) in the teaching hospital. For parenteral medication, one or more MAEs occurred in 123 of 488 administrations (25.2%) and the double check during administration was performed in 135 out of 433 parenteral administrations (35.8%). The determinant double check of parenteral medication was not significantly associated with the occurrence of MAEs (odds ratio 1.51, 95% confidence interval 0.64–3.55; adjusted odds ratio 0.90, 95% confidence interval 0.25–3.25, $n = 404$).

TABLE 3 Prevalence, type and potential severity of medication administration errors (MAEs) in two Dutch hospitals

Included medication administrations, *n*	2576
Administrations with one or more MAEs, *n* (%)	352 (13.7)
Total MAEs, *n*	380
Administrations with 1 MAE	325
Administrations with 2 MAEs	26
Administrations with 3 MAEs	1
Type of MAEs, *n* (%)	
Omission	87 (22.9)
Wrong medication handling	75 (19.7)
Wrong dose	73 (19.2)
Wrong administration technique	
Too fast administration	53 (13.9)
Incompatibility of parenteral medication	21 (5.5)
Other	6 (1.6)
Unordered drug	29 (7.6)
Wrong dosage form	28 (7.4)
Wrong route of administration	6 (1.6)
Expired medication	1 (0.3)
Other	1 (0.3)
Potential severity of MAEs[a], *n* (%)	
Error, no harm	
C	214 (56.3)
D	121 (31.8)
Error, harm	
E	36 (9.5)
F	7 (1.8)
G	0
H	2 (0.5)

[a]NCC MERP classification: no error (category A); error, no harm (category B–D); error, harm (category E–H); and error, death (category I). C: an error occurred that reached the patient but did not cause patient harm; D: an error occurred that reached the patient and required monitoring to confirm that it resulted in no harm to the patient and/or required intervention to preclude harm; E: an error occurred that may have contributed to or resulted in temporary harm to the patient and required intervention; F: an error occurred that may have contributed to or resulted in temporary harm to the patient and required initial or prolonged hospitalisation; G: An error occurred that may have contributed to or resulted in permanent patient harm; H: an error occurred that required intervention necessary to sustain life.

5 | DISCUSSION

In this prospective observational study in two Dutch hospitals with supportive electronic medication systems, MAEs were identified in one out of seven medication administrations, with one out of eight being potentially harmful. Omission, wrong medication handling and wrong dose accounted for 62% of all MAEs. This study identified several determinants associated with an increased probability of MAEs, in particular complex pharmaceutical forms, time windows

TABLE 4 Association between determinants and the occurrence of one or more medication administration errors (MAEs) without wrong time errors

	Mixed-effects logistic regression analysis			
	Univariable analysis[a]		Multivariable analysis[b]	Multivariable analysis[a]
			n = 1253	*n* = 2502
			With staff characteristics	Without staff characteristics
Determinants	***n***	**OR (95% CI)**	**Adjusted OR (95% CI)**	**Adjusted OR (95% CI)**
Medication characteristics				
Pharmaceutical form	2569			
Oral solid		Reference	Reference	Reference
Oral liquid		**5.52 (3.13–9.74)**	**3.22 (1.43–7.25)**	**4.73 (2.68–8.33)**
Infusion		**3.36 (2.25–5.02)**	**1.73 (1.02–2.94)**	**2.58 (1.71–3.89)**
Injection		**3.58 (2.38–5.39)**	**3.52 (2.00–6.21)**	**3.20 (2.08–4.92)**
Nebulising solution		1.89 (0.86–4.18)	1.49 (0.55–4.01)	1.69 (0.77–3.73)
Ointment		**12.08 (4.84–30.15)**	**10.78 (2.10–55.26)**	**14.01 (5.33–36.82)**
Suppository/enema		**3.77 (1.19–11.95)**	**6.39 (1.13–36.03)**	**3.62 (1.16–11.35)**
Miscellaneous[c]		**11.96 (5.65–25.33)**	**6.17 (1.90–20.04)**	**12.13 (5.68–25.88)**
Hospital characteristics				
Hospital type	2570			
University hospital		Reference	Reference	Reference
Teaching hospital		**0.20 (0.13–0.31)**	**0.17 (0.08–0.33)**[d]	**0.22 (0.13–0.36)**[d]
Time characteristics				
Day of the week	2570			
Weekdays		Reference	Reference	Reference
Weekend		**1.52 (1.03–2.25)**	0.84 (0.53–1.32)[e]	0.98 (0.67–1.45)[e]
Time window	2570			
7 a.m.–10 a.m.		Reference	Reference	Reference
10 a.m.–2 p.m.		**2.13 (1.40–3.25)**	**1.91 (1.06–3.46)**	**1.77 (1.14–2.74)**
2 p.m.–6 p.m.		1.53 (0.98–2.39)	1.31 (0.69–2.48)	1.13 (0.71–1.81)
6 p.m.–7 a.m.		**2.16 (1.40–3.31)**	**1.88 (1.00–3.52)**	1.33 (0.84–2.10)
Workload characteristics				
Patient-to-nurse ratio	2512	0.98 (0.90–1.06)	1.00 (0.89–1.12)	1.02 (0.95–1.11)
Interruptions	2561			
No		Reference	Reference	Reference
Yes		0.84 (0.52–1.36)	0.71 (0.32–1.57)	1.01 (0.61–1.66)
Staff characteristics				
Nursing degree type	1321			
Nurse		Reference	Reference	
Specialised nurse		**2.15 (1.07–4.34)**	1.74 (0.90–3.35)	
Other		1.76 (0.72–4.29)	1.62 (0.82–3.18)	
Educational level	1320			
Secondary vocational education		Reference	Reference	
Higher professional education		1.14 (0.65–2.01)	**1.68 (1.03–2.74)**	
Other		1.56 (0.62–3.90)	1.47 (0.67–3.22)	

(Continues)

TABLE 4 (Continued)

	Mixed-effects logistic regression analysis			
	Univariable analysis[a]		Multivariable analysis[b]	Multivariable analysis[a]
			n = 1253	*n* = 2502
			With staff characteristics	Without staff characteristics
Determinants	***n***	**OR (95% CI)**	**Adjusted OR (95% CI)**	**Adjusted OR (95% CI)**
Experience in healthcare settings	1315			
0–1 year		1.11 (0.11–11.04)	0.91 (0.20–4.17)	
1–5 years		0.83 (0.48–1.45)	0.84 (0.52–1.35)	
More than 5 years		Reference	Reference	
Employment type	1301			
Non-temporary		Reference	Reference	
Temporary		0.72 (0.30–1.74)	1.11 (0.55–2.25)	

Note: Odds ratios in bold have a p value < .05.

Abbreviations: CI, confidence interval; OR, odds ratio.

[a]Mixed-effects logistic regression analyses were used to account for within-subject correlations due to repeated measurements by staff member and patient.

[b]Mixed-effects logistic regression analyses were used to account for within-subject correlations due to repeated measurements by patient.

[c]Miscellaneous: eye drops, eye gel, inhalation aerosol or powder, intestinal gel, nasal spray, patch.

[d]Represents the OR during weekdays.

[e]Represents the OR for the university hospital (the teaching hospital did not include weekend administrations).

10 a.m.–2 p.m. and 6 p.m.–7 a.m., and nurses that had received higher professional education. Also, MAEs were more likely to occur in the university hospital compared to the teaching hospital.

MAEs were identified in 352 of 2576 administrations (13.7%), which proportion corresponds well with existing literature. A systematic review of Berdot et al., 2013 reports a median MAE rate of 10.5% (IQR 7.3%–21.7%) (Berdot et al., 2013), while Keers et al., 2013 show a median error rate of 8.0% (IQR 5.1%–10.9%) (Keers et al., 2013b). The distribution of MAE types and severity scores in our study also correspond well with these studies. However, it should be noted that the extensive clinical and methodological heterogeneity between studies (e.g. differences in ward types, administration procedures, electronic medication systems, data collection methods, studied error types) makes it difficult to compare findings of different MAE or MAE determinant studies.

Almost all pharmaceutical forms were associated with an increased probability of MAEs compared to oral solids. Most of these forms require additional steps within the administration process (e.g. shaking suspensions, calculating volumes or tuning infusion pump settings). Each additional step introduces an extra opportunity for error. Especially parenteral medication has been widely associated with an increased risk of errors (Keers et al., 2013b; Nguyen et al., 2015). A remarkable finding was that many injections, for example furosemide, granisetron and dexamethasone, were administered substantially faster than the recommended administration rate, usually within a few seconds, even though the maximum administration rates are specifically addressed in the electronic local protocols, which were easily accessible from any computer. This issue was also addressed in other studies (Ong & Subasyini, 2013; Sutherland et al., 2020; Taxis & Barber, 2003; Westbrook et al., 2020) and suggests that nurses may not know the maximum administration rate or assume deviating from it to be not clinically relevant (Keers et al., 2013a; Schroers et al., 2020). Some of the pharmaceutical forms, such as ointments and inhalation aerosols, seemed to be more susceptible to omission. An explanation may be that these medications are usually not considered the most necessary during hospitalisation. Interventions targeting the relatively complex, that is error-prone, pharmaceutical forms may include support from pharmacy staff to perform medication handling tasks using standard protocols, increased use of ready-to-administer medication (Kuitunen et al., 2021b), smart infusion pumps (Kuitunen et al., 2021b) and educational programmes for nurses, for example by simulation-based training (Keers et al., 2014). The first two strategies have the ability to reduce the frequency of errors related to medication handling, wrong dose, wrong dosage form and fast administration (i.e. when supplying infusions rather than concentrated solutions). Smart infusion pumps with a drug library have been shown to reduce the number of wrong infusion rates and wrong doses when used properly (Kuitunen et al., 2021b).

The probability of MAEs was lower in the teaching hospital compared to the university hospital. Many factors, such as local workplace factors (e.g. technology, culture, medication supply and

dispensing, local training programmes), may play a role, but also lower patient and medication complexity in the teaching hospital could partly explain this finding (Keers et al., 2013a). The higher proportions of included anti-infective medication (5.8% vs. 15.0%) and parenteral medication (11.3% vs. 25.2%) in the university hospital support this explanation. Another explanation is that the teaching hospital had already implemented barcode verification of parenteral medication, which may have prevented some types of errors, as barcode technology has been shown to be effective (Hutton et al., 2021). Other hospital differences include the type of medication management system (Epic® vs. HiX®) and the medication cart filling procedures (by pharmacy staff in the teaching hospital versus nursing staff in the university hospital). The university hospital moved to a completely new hospital in May 2018, which entailed many new procedures for nursing staff. Additionally, although strict review protocols were in place to minimise variations in reviewer assessments, differences between the reviewing teams of the two hospitals cannot be ruled out.

MAEs were more likely to occur between 10 a.m. and 2 p.m. and between 6 p.m. and 7 a.m. compared to the early morning. This may be related to factors such as workload, the uneven distribution of tasks during the day, and vigour or fatigue of nursing staff. Especially administration during the night shift has been previously reported as error-prone (Feleke et al., 2015; Wondmieneh et al., 2020), as the lack of circadian adaptation to night work may lead to impaired alertness and performance (Ganesan et al., 2019). These time-related determinants warrant a critical review of the daily routines in relation to standard medication administration rounds and workload distribution during the day. This may lead to insights on preferred standard medication administration times tailored to a specific clinical ward. Support by pharmacy staff, for example for medication handling tasks or dispensing in patient medication cabinets, may have benefits by decreasing the workload or time constraints of nursing staff, as these factors have been extensively associated with MAEs (Keers et al., 2013a, 2015; Kuitunen et al., 2021a; Parry et al., 2015; Schroers et al., 2020). In general, additional benefits may be gained by active engagement of nurses to tailor interventions to their own practice (Alomari et al., 2020).

Unexpectedly, higher professional education was significantly associated with an increased MAE probability. This finding may be related to the degree of confidence or tendency to make assumptions (Schroers et al., 2020), but the true causes remain to be explored. Data on nursing staff characteristics were unavailable in approximately 45% of observations; therefore, this finding should be interpreted with caution. Earlier studies on determinants related to nursing staff characteristics have shown conflicting results (Feleke et al., 2015; Nguyen et al., 2015; Prot et al., 2005; Rodriguez-Gonzalez et al., 2012).

In contrast to several previous studies, no significant associations were found for the determinants day of the week (Harkanen et al., 2015, Nguyen et al., 2015, van den Bemt et al., 2002), patient-to-nurse ratio (Berdot et al., 2012; Feleke et al., 2015) and interruptions (Blignaut et al., 2017; Feleke et al., 2015; Harkanen et al., 2015; Westbrook et al., 2010; Wondmieneh et al., 2020). However, a study of Berdot et al. (2012), which was conducted in a setting similar to our study, also did not find significant associations for day of the week and for interruptions. Many MAEs in our study did not seem accidental mistakes, but rather routinely occurring deviations as identical errors occurred repetitively, particularly too fast administration of intravenous medication or mixing all oral medications for administration by a feeding tube. This finding may explain the lack of association between interruptions and MAEs in this setting. With regard to patient-to-nurse ratio, our study is not the first showing a lack of association with MAEs (Rodriguez-Gonzalez et al., 2012). Patient-to-nurse ratio is a commonly used proxy for workload, but it does not take all relevant workload-related factors into account, such as disease severity and non-patient related tasks (Carayon & Gurses, 2008; Griffiths et al., 2020).

The finding that several MAEs occurred repetitively emphasise the need for additional and tailored systemic defences, especially technological barriers, to prevent MAEs. For example, smart infusion pumps with hard limits that cannot be overridden will prohibit too fast administration of intravenous medication. Additionally, barcode-assisted medication administration using hard stops in case of scanning the wrong medication or patient will prevent wrong drug, wrong dose and wrong dosage form errors (Hutton et al., 2021). Workarounds need to be prevented, as they may compromise the beneficial effects of scanning (Mulac et al., 2021; van der Veen et al., 2018). Also increasing nurses' knowledge (e.g. by embedding additional medication education in nursing undergraduate and postgraduate curricula) and increased accessibility to necessary information (e.g. directly in the eMAR) may help to reduce the associated risks. This study was performed before the planned comprehensive operations to improve medication safety in both hospitals. Thus after conducting this study, both hospitals optimised their medication process by implementing several interventions, including automated unit-dose dispensing and barcode-assisted medication administration (Jessurun et al., 2021).

5.1 | Strengths and limitations

A strength of this study is that, to our knowledge, this is the first study on the determinants of MAEs in a setting with an EMR, a CPOE and an eMAR system in place. Also, we investigated medication administrations to inpatients in 11 clinical wards in two hospitals and examined many types of medication administrations performed by more than 200 nursing staff members, supporting the generalisability of the results of this study to similar hospitals. Additionally, we used a robust method to assess MAEs and analyse determinants of MAEs.

This study has several limitations. First, observer and reviewer bias may have occurred, even though the disguised observation method is the gold standard to detect MAEs (Allan & Barker, 1990; Dean & Barber, 2001). Several measures have been taken to limit observer and reviewer bias, such as comprehensive training programmes for observers and protocols for reviewers. Second, timing

errors were excluded because these errors occur frequently (Berdot et al., 2013; Keers et al., 2013b), while being considered not clinically relevant in many cases. This could be debated because these errors may be clinically relevant for time-sensitive medication and important from a system-failure perspective (Allan & Barker, 1990). However, the possibility of an exceptionally high error rate may hamper determinant analysis. Third, we measured potential harm instead of the actual harm to patients. Fourth, fewer determinants were tested than initially planned to prevent overfitting of the multivariable mixed-effects model. For instance, hospital type was chosen instead of clinical ward type in order to decrease the number of variables to be tested and because MAE rates were comparable for the clinical wards in the same hospital. Last, we may have addressed several determinants insufficiently, such as personal factors (e.g. stress levels and job satisfaction), patient factors (e.g. clinical condition) and environmental factors (e.g. noisy environment) (Carayon & Gurses, 2008; Keers et al., 2013a, 2015; Kuitunen et al., 2021a; Parry et al., 2015; Schroers et al., 2020).

5.2 | Further research

Future studies should focus on the determinants insufficiently addressed in our study and should include measurement of clinically relevant outcomes.

6 | CONCLUSION

In the two hospitals with supportive electronic medication systems (i.e. EMR, CPOE and eMAR), MAEs occurred in 352 of 2576 administrations (13.7%), with one out of eight having the potential to lead to patient harm. The determinants identified in this study indicate that the complexity of pharmaceutical forms, working conditions and complex patient populations are contributing factors. Strategies to reduce the occurrence of MAEs and therefore to optimise patient care should target the identified determinants and focus on systemic defences to prevent structural errors.

7 | RELEVANCE TO CLINICAL PRACTICE

Medication errors are major contributors of preventable patient harm globally. In this study, we showed that MAEs, including harmful errors, are prevalent in modern care, even with several supportive electronic medication systems in place. Additional preventive strategies are needed to tackle this issue. The determinants identified in our study can be used to develop targeted strategies and interventions to improve patient safety across similar hospital settings.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

JJ, NH, MD and PB contributed to the conception, data collection, data analysis and writing of the manuscript. JM contributed to the conception, data analysis and writing of the manuscript. MR and HO contributed to the data collection and writing of the manuscript. All authors read and approved the final manuscript.

ETHICAL APPROVAL

The Medical Ethics Review Committee of Erasmus MC waived approval for this study (reference number MEC-2018-1532) in accordance with the Dutch Medical Research involving human subjects Act.

DATA AVAILABILITY STATEMENT

The dataset generated and analysed during the current study is available from the corresponding author on reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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