MEDICATION ERRORS IN THE OUTPATIENT AND AMBULATORY SETTINGS: AN EVIDENCE SYNTHESIS APPROACH

by

LINA NASERALALLAH

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Sir Robert Aitken Institute for Medical Research

School of Pharmacy

College of Medical and Dental Sciences

University of Birmingham

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Abstract

Background: Medication errors are preventable incidents that may occur at any stage of the medication use process. Despite their potential to cause severe harm, they are common in healthcare settings. Outpatient and ambulatory settings are known to enhance patient access to healthcare and promote continuity of care. Medication therapy remain key interventions offered in these settings. Currently, there is a dearth of literature on the prevalence and contributory factors to medication errors in the outpatient setting.

The program of work presented in this thesis firstly, through the use of an umbrella review, aims to systematically evaluate the contributory factors to medication errors in healthcare settings in terms of the nature of these factors; methodologies and theories used to classify them; and terminologies and definitions used to describe them. The second phase of the thesis aims to synthesize the literature on the prevalence, nature, contributory factors, and interventions to minimize medication errors in outpatient and ambulatory settings using a systematic review of research literature.

Methods: In the first phase, an umbrella review was conducted. Systematic reviews were searched using Medline, Cumulative Index of Nursing and Allied Health Literature (CINAHL), Embase, and Google Scholar from inception to March 2022. The data extraction form was informed by the Joanna Briggs Institute (JBI) manual and critical appraisal was conducted using the JBI quality assessment tool. A narrative approach to data synthesis was adopted.

In the second phase, a systematic review was conducted. Literature was searched using Medline, Embase, CINAHL, and Google Scholar from 2011 to November 2021. Quality

assessment was conducted using the quality assessment checklist for prevalence studies tool. Data related to contributory factors were synthesized according to Reason's Accident Causation Model.

Results: Twenty-seven systematic reviews were included, most of which focused on a specific healthcare setting or clinical area. Decision-making mistakes such as non-consideration for patient risk factors most commonly led to error, followed by organizational and environmental factors (e.g. understaffing and distractions). Only ten studies used a prespecified methodology to classify contributory factors, among which the use of theory, specifically Reason's theory was most common. None of the reviews evaluated the effectiveness of interventions in preventing errors.

Twenty-four articles were included in the systematic review. Medication errors were common in outpatient and ambulatory settings. A wide range of prevalence of prescribing errors and dosing errors was reported with errors ranging from 0-91% and 0-41% respectively of all medications prescribed. Latent conditions largely due to inadequate knowledge were common contributory factors followed by active failures. The seven studies that described the use of interventions were of poor quality.

Conclusion: The findings of this program of work provides a comprehensive list of contributory factors to medication errors in healthcare settings. It also emphasizes on the need for consistent use of terminology and methodology in researching contributory factors. The systematic review reports the prevalence and contributory factors to errors in outpatient setting. This thesis overall, emphasizes the need for multifactorial theory-based interventions that incorporate system-level strategies, pharmacists, technology, and education to minimize medication errors in all healthcare settings.

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Under review in the International Journal of Clinical Pharmacy Journal (impact factor: 2.305).

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List of abbreviations

Abbreviation	Term
ADE	Adverse drug events
AHRQ	Agency for Healthcare Research and Quality
AMSTAR 2	Assessment of multiple systematic reviews 2
ASHP	American Society of Health-System Pharmacists
CASP	Critical Appraisal Skills Programme
CDC	Center of Disease Control and Prevention
CFIR	Consolidated Framework for Implementation Research
CI	Confidence intervals
CINAHL	Cumulative Index of Nursing and Allied Health Literature
CPI	consumer price index
CRD	Centre for Reviews and Dissemination
Emtree	Embase Subject Headings
E-prescribing	Electronic prescribing
EQUATOR	Enhancing QUAlity and Transparency Of health Research
FDA	Food and Drug Administration
FIP	International Pharmaceutical Federation
FRAM	Functional Resonance Accident Model
IOM	Institute of medicine
ISLAGIATT	It Seemed Like A Good Idea At The Time principle
JBI	Joanna Briggs Institute
MARQ	Metareview Assessment of Reporting Quality
MeSH	Medical Subject Headings
MOOSE	Meta-analysis Of Observational Studies in Epidemiology
MRC	Medical Research Council
NAM	National Academy of Medicine
NCCMERP	National Coordinating Council for Medication Error Reporting and Prevention
NHS	National Health Service
NLM	National Library of Medicine’s
NMP	Non-medical prescribing
NPSA	National Patient Safety Agency
NRLS	National Reporting and Learning Systems
NSAIDs	nonsteroidal anti-inflammatory drugs
PHCC	Primary healthcare centers
PRIO-harms	Preferred reporting items for overviews of systematic reviews
PRIOR	Preferred reporting items for overviews of reviews
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PRISMA-P	Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension for Protocols
PRISMA-S	Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension for Searching
PRISMA-ScR	Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension for Scoping Reviews
PROSPERO	International Prospective Register of Systematic Reviews
PSI	Patient safety incidents
STAMP	Systems-Theoretic Accident Model and Process
STROVI	Standards for reporting of overviews of reviews and umbrella reviews
QCRI	Rayyan Qatar Computing Research Institute
TDF	Theoretical Domain Framework
UK	United Kingdom
US	United States
WHO	World Health Organization

Chapter 1: Introduction

This chapter will provide introduction to the thesis. Key terminologies such as definition and scope of medication errors, outpatient and ambulatory settings, and accident causation theories will be presented. The types, prevalence, and consequences of medication errors based on the available literature will be discussed thoroughly. The chapter concludes with the presentation of the aim and objectives for the MSc by research project.

1.1 Definition of medication errors

Over the past few decades, several attempts have been made to offer a standard definition of medication errors. Currently however, there does not appear to be one agreed definition of this phenomenon. An etymological approach is a technique to define medication errors by simply defining the terms in it; medication and error (1). Aronson and Ferner (2) defined medication as “medicinal product that contains a compound with proven biological effects, plus excipients, or excipients only; it may also contain contaminants; where the active compound is usually a drug or prodrug but may be a cellular element”. The term ‘error’ has been defined by the Institute of Medicine (IOM) as “a failure to complete a planned action as intended, or the use of an incorrect plan of action to achieve a given aim” (3). Although it is crucial to understand the literal meaning of the words, it is still required to appreciate the nomenclature in the context of its utility. Definitions proposed by different committees and experts should also be taken into consideration.

A systematic review investigating the various definitions of medication errors captured in the literature revealed multiplicity, with 45 generic definitions and 26 different wordings (4). Of the 45 studies included in this review, five studies, all published in 2005 or before, encompassed “deviation” in the administered regimen from the written prescription. The latter is considered an old definition that was initially proposed by Barker et al (1982) and then slightly amended to also include deviation from hospital policies and manufacturers labels (5-7). Additionally, 20 studies incorporated one or more stages of the medication use process (prescribing, transcribing, dispensing, administering, and monitoring) in their definition (4). Of which, 15 studies combined the medication use process with the term “error” while five used “failure” (4). Bates et al (1995) initially suggested the use of the medication use process in the definition of medication errors and it was extensively used thereafter (8). Three miscellaneous definitions were also identified, and they utilized terms such as mistakes or omission. For instance, Miller and colleagues (2006) proposed the following definition “an act or omission (involving medication) with potential or actual negative consequences for a patient that based on standard of care is considered to be an incorrect course of action” (9).

As part of the effort to develop a standardized international definition of medication errors, the National Coordinating Council for Medication Error Reporting and Prevention (NCCMERP) in the United States (US) published a definition (Table 1.1) that has been widely acceptable and extensively utilized in the literature (10). This definition can be distilled into four main concepts: (1) avoidability of the error; (2) alternative nomenclature

for medication errors; (3) potential consequences; and (4) stages in which the error can take place.

The American Society of Health-System Pharmacists (ASHP) articulated their own definition of medication errors in 1993 (Table 1.1); however in their 2018 update they adapted the NCCMERP definition (11, 12). Other key professional/policy organizations have also adapted the NCCMERP definition which includes, but not limited to, the International Pharmaceutical Federation (FIP) in 1999, the Department of Health in the United Kingdom (UK) in 2004, the Council of Europe in 2005, the Institute for Safe Medication Practices, the Food and Drug Administration (FDA), and the World Health Organization (WHO) (10-16).

There has been however, critique of the NCCMERP definition despite its wider adoption. In 2000, Ferner and Aronson proposed a definition (Table 1.1) to overcome a gap identified in the NCCMERP definition. The proposed gap suggested that preventable events could still occur even after an evidence-based decision to use a medication associated with unpreventable harm (e.g. azathioprine-induced bone marrow suppression) (17, 18).

The Australian Council for Safety and Quality in Health Care have utilized and modified Ferner and Aronson definition (17, 18). The former also referred to medication errors as “failure”, with slight modification to contain the act of omission and commission (19, 20). Error of omission refers to the unauthorized skipping of a scheduled dose. Error of commission refers to the discrepancy between the administered and ordered doses in any of the prescription components (e.g. name, strength, or dose) (17). It is worth noting

that, unlike the NCCMERP definition, these two definitions did not reflect on the preventability of medication errors nor included the stages in which they could occur.

A study conducted to investigate definitions of safety terminology by 160 international organizations revealed seven different definitions for medication errors (21), two of which are captured earlier. In parallel with the Australian Council for Safety and Quality in Health Care, the Agency for Healthcare Research and Quality (AHRQ) of the US incorporated error of commission and omission in their definition (22). However they used the term “error” instead of “failure”. Whilst they mentioned that these errors can take place at any phase from prescribing to dispensing, they did not describe the detailed steps nor included monitoring measures. Their definition also lack the preventability and impact components (22).

The National Reporting and Learning Systems (NRLS) established by the National Patient Safety Agency (NPSA) in the UK, referred to medication errors as a “patient safety incidents (PSI)”. In their definition they also included the stages of the medication use process. The NPSA stated that events are still counted as medication errors regardless of harm occurrence and they excluded the avoidability element from the definition (23).

Health Canada utilized the terms medication errors and incidents interchangeably and defined it as “a mistake or a problem that could cause a mistake”. Although they have provided examples of the stages in which errors could occur, they did not set out all the steps. This definition has integrated the avoidability component, but not the consequences component (24).

The American National Academy of Medicine (formerly called IOM) produced a shorter and simplified version of the NCCMERP definition. This definition eliminate the mention of preventability, detailed stages for error occurrence, and outcomes of these errors (25).

Table 1. 1 Medication errors definitions according to safety bodies

Organization or author	Definition
National Coordinating Council for Medication Error Reporting and Prevention (NCCMERP), 1996	Any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the healthcare professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems, including prescribing, order communication, product labelling, packaging, and nomenclature, compounding, dispensing, distribution, administration, education, monitoring, and use (10).
Dean B, 2000	A reduction in the probability of treatment being timely and effective, or an increase in the risk of harm relating to medicines and prescribing compared with generally accepted practice (26).
American Society of Health-System Pharmacists (ASHP), 1993	Episodes in drug misadventuring that should be preventable through effective systems controls involving pharmacists, physicians and other prescribers, nurses, risk management personnel, legal counsel, administrators, patients, and others in the organizational setting, as well as regulatory agencies and the pharmaceutical industry (11).
Ferner R and Aronson J, 2000	Failure in the treatment process that leads to, or has the potential to lead to, harm to the patient (18).
Australian Council for Safety and Quality in Health Care	Failure in the (drug) treatment process that leads to or has the potential to lead to, harm to the patient and includes an act of omission or commission (20).
Agency for Healthcare Research and Quality (AHRQ)	An error (of commission or omission) at any step along the pathway that begins when a clinician prescribes a medication and ends when the patient actually receives the medication (22).
National Patient Safety Agency (NPSA)	Patient safety incidents involving medicines in which there has been an error in the process of prescribing, dispensing, preparing, administering, monitoring, or providing medicine advice, regardless of whether any harm occurred (23).
Health Canada	A mistake with medication, or a problem that could cause a mistake with medication. Medication incidents are generally preventable and include errors like receiving the wrong medication or dose, or using the wrong route of administration (24)
Institute of Medicine (IOM), 1999	Any error occurring in the medication-use process (25).

1.2 Classification of medication errors

Multiple approaches have been implemented to classify medication errors including the sequence in the medication use process, the etiology of the error, the outcome of this error, and the factors contributing to this error.

1.2.1 Classification according to the stage in the medication use process

Baker et al (1982) suggested that failure could occur at any step of the medication system; hence medication errors can be categorized accordingly to error in diagnosis, prescription writing, prescription receiving and processing, dispensing, administration, and patient receiving the medication (6). Whilst this classification may be preliminary compared to the current rising understanding of medication errors, it could be considered suitable for the definition adapted by the authors which merely focuses on variation from written orders.

A later article classified medication errors into three broad categories, prescribing, dispensing, and administration with further detailed subsets under each category (27). A succinct version of this classification that depended on a more comprehensive understanding of the medication use process evolved and has been extensively used in the literature. This updated version includes transcribing and monitoring in addition to the previously stated stages (17, 28).

1.2.2 Classification according to the type/nature of the error

Another mechanism for classification relies on the incident type. Classification suggested by Hynniman et al (1970) incorporated three main groups: omission; commission; and discrepancies (29). Other studies have articulated a more thorough classification that

includes the exact nature of the incident including wrong quantity; incorrect patient; duplicate therapy; contraindication; wrong/omitted verbal patient direction; wrong dose/strength; wrong drug; and missed drug/omission (5, 30-33).

Some medication safety organizations, such as the American ASHP, also suggested taxonomies of medication errors based on the nature of these errors (34). However, to date, there is no agreed classification, and each study reports a different set of categories. For instance, some studies reported classes retrieved by determining the common recurring events, while others adapted a classification from previously published papers (30, 35).

1.2.3 Classification according to the consequences/outcomes of the error

The nine-category Medication Error Index proposed by the NCCMERP is a third method for classifying medication errors depending on the harm they caused or may have caused (10). These nine categories fall under four explicit groups: no error; error but no harm; error with harm; and error with death (Figure 1.1).

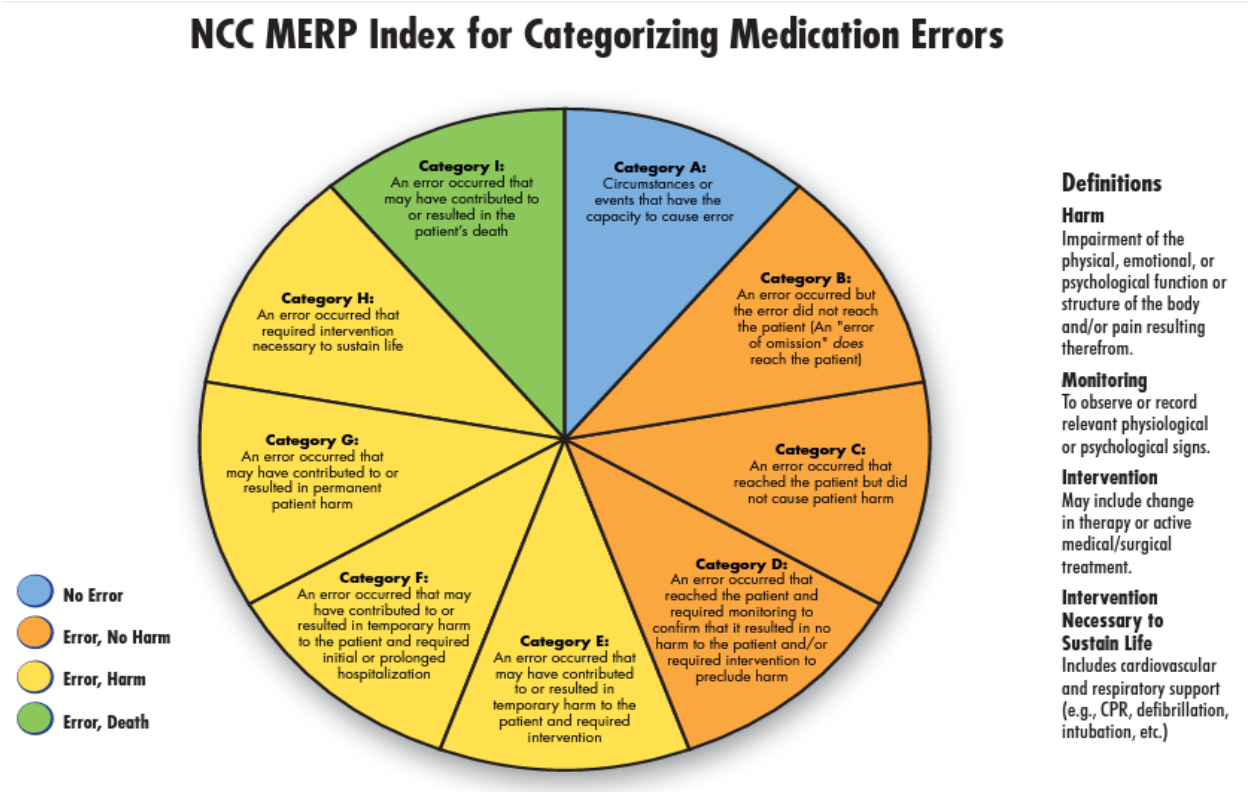

Figure 1. 1 NCCMERP Index for categorizing medication errors (NCCMERP, 1996)

Severity scales is another method for classifying errors according to their outcomes; however, a variety of severity assessments have been identified in the literature with a lack of consensus regarding what exactly constitutes a severity scale. For example, Bate et al (1995) had four classifications (significant, serious, life-threatening, and fatal), while Alagha et al (2011) applied a simpler classification that consisted of mild, moderate, and severe (36, 37).

1.2.4 Classification according to contributory factors

A novel approach to classifying medication errors could be the psychological analysis to identify antecedent contributory factors to an incident. Identifying and classifying

contributory factors is especially important as understanding these factors will facilitate the development of potentially effective preventative measures. Several approaches have been suggested to investigate contributory factors, including Reason's Accident Causation Model (38). This topic is further discussed below in section 1.5.

1.3 Regional and national prevalence of medication errors

Medication errors are costly and common events across the globe (39). Although it is believed that medication errors are underreported, the official national declared rates of their occurrence are alarming and necessitate interventions to reduce their occurrence. These numbers were found to be consistently high in multiple countries across different continents. For instance, estimates based on the IOM showed that medication errors affect a population of 7 million hospitalized patients in the US alone with costs from $17 to $21 billion per year to manage the affected patients (3). In addition, in 2006, the US National Academy of Medicine (NAM) declared that more than 1.5 million people are injured every year due to medication errors totaling more than $7 billion (25).

In England, medication errors rates remain significantly high with staggering associated costs. Despite the various interventions implemented to mitigate medication errors, the National Health Service (NHS) estimated that 237.3 million errors occur every year with 66 million considered potentially clinically significant (40). The cost of preventable adverse drug events (ADE) continues to be a hefty economic burden on the NHS as it reached £98 462 582 annually according to a report published in 2020 (41).

In the Middle East, there is paucity of data about the prevalence of medication errors on a national level; however some studies have investigated the rates in segments of the population. For instance, a retrospective review of the reports submitted from the governmental sector only (hospitals and primary healthcare centers [PHCC]) to the national medication error database in Saudi Arabia showed that 71, 332 incidents were reported in the period between March 2018 to June 2019. Of these, 6.8% errors were associated with patient harm (42).

1.4 Consequences of medication errors

The consequences of medication errors could range from no obvious patient harm to severe harm and mortality. Although it is estimated that only 10% of medication errors results in ADE, their occurrence has been associated with serios deleterious impact on patients' health outcomes, families, healthcare providers, and healthcare systems (8).

1.4.1 Impact on patient health outcomes

One of the profound implications associated with medication errors is the significant increase in morbidity, some of which is irreversible (43). A review that focused on medication errors in the acute care settings in Australia reported that 2-3% of hospital admissions were medication-related (19). The estimate point was generated from Australian literature published from 2008 to 2013. However, the authors still obtained data from the two major previous reviews from Australia in 2002 and 2008 (44, 45).

A matched case-control study demonstrated that the length of hospital stay has also increased by 1.74 days for patients experiencing error-related ADE during their

hospitalization (43). This was a single center study from a hospital in the US with a three-year follow-up period. Matching was done based on age, gender, discharge diagnosis, acuity, and year of admission.

An England-based study that estimated the burden of medication errors to the NHS showed that in one year, 712 error-related deaths occurred, and it is believed that they also contributed to 1708 deaths and occupied 181 626 bed-days (41). It is worth pointing out that these estimates relied mainly on retrospective judgment of the occurrence of harm and the preventability of the event. Non-UK data have also been used to supplement this synthesis in scenario analyses.

1.4.2 Economic consequences of medication errors

Medication errors could impose a heavy financial burden on healthcare systems. Globally, they are estimated to cost $42 billion every year according to the WHO (39). A systematic review including 15 studies reported that the average cost of one medication error ranged from € 2 to €111 727 (46). In this review data were transformed using the consumer price index (CPI) for medical and non-medical services for each country in order to express all values in a common numerical value (Euro 2015) and account for the inflation rate (46). Other medication errors-related monetary costs are presented in section 1.3.

1.4.3 Psychological impact

The psychological impact of medication errors on patients, families, and health practitioners is often underestimated. Medication errors could erode the confidence of patients and their families in their healthcare providers and the organizations that hired

them (47). When such events become publicly available, they could also negatively impact the public trust in the healthcare system.

Physicians who committed errors might suffer from pronounced emotional distress and job-related stress following the incident (48). This was demonstrated in a survey study conducted in the US and Canada on 4990 physicians with 63.5% response rate (48). The study focused on physicians who committed any type of medical errors; hence it was not specific to medication errors. The recruited physicians were from various specialties including internal medicine, family medicine, pediatrics, and surgery. The questionnaire instrument was developed by experts in patient safety and survey design following a literature review and physician cognitive interviews.

The results of this study were consistent with another retrospective survey study conducted on multiple health practitioners. The latter included 913 clinicians (physicians, nurses, and midwives) and investigated safety incidents in general using a verified tool (Impact of Event Scale) (49). This study demonstrated that practitioners could experience deep sense of personal failure, significant guilt that they were unable to provide optimum care to their patients, anxiety about future mistakes, sleeping problems, decreased job satisfaction, and reputation damage (48, 49).

1.5 Using causation models in medication errors investigation

Synthesis of contributory factors (introduced in section 1.2.4) to medication errors is one of the methods that has been discussed to increase the understanding of medication

errors. Synthesizing and understanding the factors contributing to errors enables policy-makers and healthcare providers to design interventions tailored to mitigate these factors which subsequently could effectively reduce medication errors (50).

A plethora of conceptual models have been developed to analyze events for the purpose of ascertaining contributing factors. Accident causation frameworks are theoretical models that have been widely implemented to conceptualize and associate the determinants and consequences of accidents taking place in any aspect of a human life including healthcare (51, 52). These models can be classified into three classes: (1) linear simple models; (2) linear complex models; and (3) non-linear complex models.

1.5.1 Simple linear models

The sequential or event-based accident modelling purports that any incident is the outcome of a series of events occurring in a chronological order (52). This theoretical foundation underpins most causality models as it makes the model practical and easy to use (51).

Heinrich et al (1931) proposed the Domino theory (Figure 1.2), which represent the first causation model. This theory suggested that all incidents are the outcome of a chain of events (dominoes). To prevent a mishap from taking place, one of these dominoes should be removed, typically one of the middle dominoes or the one identified to be an unsafe act (53).

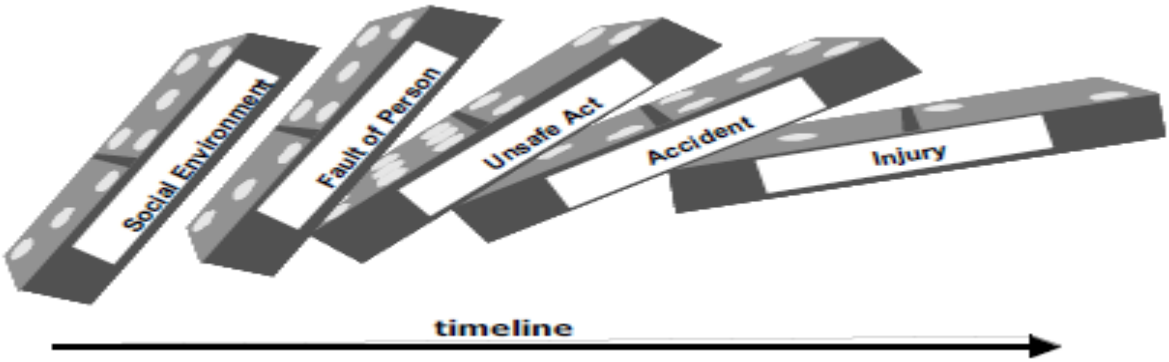

Figure 1. 2 Domino model of accident causation (Heinrich et al., 1931)

Bird and Germain developed the International Loss Control Institute (ILCI) model (Figure 1.3) in 1985. This model proposed updates to the Domino theory to make it more comprehensive. It also was the first to introduce the concept of managerial errors (54).

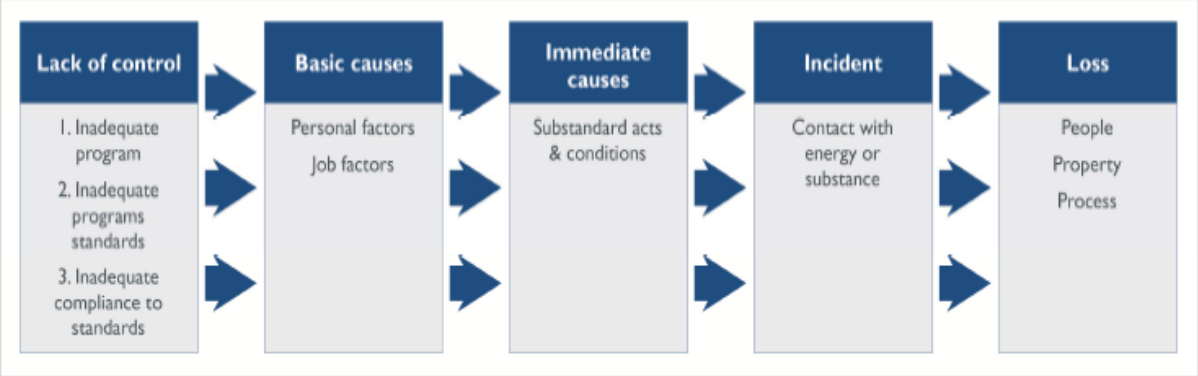

Figure 1. 3 The International Loss Control Institute (ILCI) model (Bird et al., 1985)

Several other frameworks were also proposed, following the same one-dimensional theorem. This includes: (1) the forward sequenced analysis (failure modes and effects analysis (FMEA) and fault tree analysis (FTA)); (2) the backward sequenced analysis (event tree analysis); and (3) the cause-consequence analysis (which could be performed

in both directions) (51, 55). Unlike the single chain Domino theory, some models (e.g. event tree analysis) adapted event-based accident modelling which incorporate multiple chains of events with conditional probabilities assigned to each event (56).

Whilst these models could be of sufficient effectiveness in analyzing simple systems, they do not function well in more complex systems that are becoming more common (51, 57). Most current systems are multifactorial which implies that multiple causation theory could be more appropriate. This also applies to the advanced healthcare systems as they are of high complexity.

The complexity of modern healthcare systems could be due to the technological advances (e.g. pharmacy automation). Technologies can in one hand mitigate medication errors by reducing traditional human errors; on the other hand, they might introduce new unknown hazards to systems (57, 58). The accelerated technological changes also have the potential to create more complex relationships between humans and automation systems. New types of human errors (e.g. mode confusion) hence are known to appear, and the distribution of incident types associated with human errors could also change (e.g. higher proportion of omission as compared to commission errors) (57). In addition, the advanced therapeutic approaches (e.g. chemotherapy or transplantation) that followed the increased understanding of the pathophysiology of diseases, exposed an increasing size of the population to risks and errors (59-61). Lastly, it is suggested that health systems have intrinsic complexity owing to multiple factors including the dynamic processes and the concomitant involvement of multiple practitioners with integral roles amongst others (62).

1.5.2 Complex linear models

To overcome the drawbacks in simple linear models (section 1.5.1), epidemiological accident models were developed in the second half of the 20th century (51). They presume that accidents are the culmination of a combination of manifest and latent contributory factors, occurring in a linear fashion (51, 52). Factors taking place at the beginning are organizational or environmental factors, while factors happening towards the end are human factors, who interact directly with the system (52). To prevent incidents from occurring, appropriate controls should be set to strengthen barriers and defense mechanisms (52).

Some of the key models that adapted the complex linear design are the energy damage models, time sequence models, generic epidemiological models, and models of systems safety (52). Table 1.2 provides a brief discerption of each of these models.

Table 1.2 Key models that adapted the complex linear design

Model	Supposition/description
Generic epidemiological models, 1949	Accidents are caused by a combination of forces from at least three sources, which are the host (man is the host of principal interest), the agent itself, and the environment in which host and agent find themselves
Energy damage models, 1961	Damage (injury) is a result of an incident energy whose intensity at the point of contact with the recipient exceeds the damage threshold of the recipient
Time sequence models, 1975	These models have four requirements: (1) define a beginning and end to an accident; (2) represent the events that happened on a sequential timeline; (3) structured method for discovering the relevant factors involved; and (4) use a charting method to define events and conditions
Models of systems safety, 1984	Models had to reflect realism as the true nature of the observed accident phenomenon. A realistic accident model must reflect both a sequential and concurrent nonlinear course of events, and reflect events interactions over time

Reason's "Swiss Cheese" model (Figure 1.4) was one of the early models that recognized the systemic environment influence on accident phenomenon. By doing so, the system moves from appointing blame to human errors, to a no-blame culture that aims to understand the multiple factors occurring at different levels of the system and contributing to an incident. This model provides an insight into possible methods of preventing accidents by eliminating contributory factors while previous models have limited usability in term of avoidability (63).

Figure 1. 4 Reason's "Swiss Cheese" model of accident causation (Pryor P et al., 2012)

This model was proposed in 1997 and has been largely applied for reporting contributory factors in several fields ever since (38). It divides the contributory factors into two broad categories (Figure 1.5), active failure (person approach: unsafe acts committed by frontliners), and latent conditions (system approach: system failures attributed to top level management decisions) (64). Active failure could be further grouped into slips (error of attention), lapses (error of memory), fumbles (error of execution), mistakes (decision-making), and procedural violations (intentional rule breaking). These components were presented in a comprehensive model entitled "the Reason Model of Systems Safety" (Figure 1.5) (65).

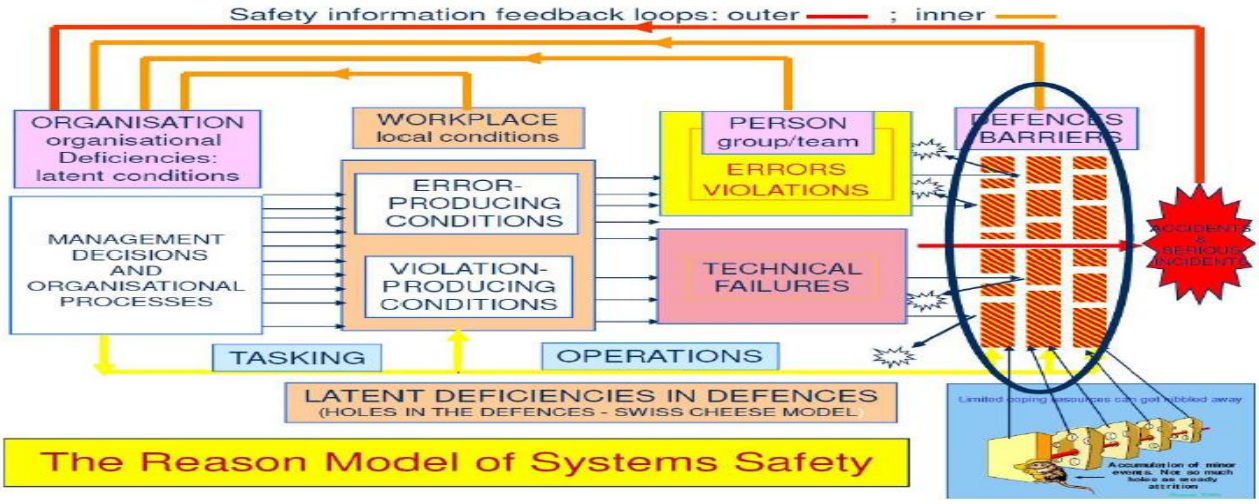

Figure 1. 5 The Reason Model of Systems Safety (Reason, 1997)

Although Reason's model could be considered a milestone in accident causation modelling, it has been criticized for not defining the metaphor of cheese slices and holes, which could make it challenging to apply it in real life scenarios (66). The other critique related to linear models is the static view of the organization assumed in these models. This does not align with the dynamic nature of accident causation in which multiple mutually interacting variables in real time environment contribute to an event (51, 52, 66). Regardless, Reason's model is still considered a fundamental causation model and it has been extensively applied in safety science in various sectors including healthcare (67-70). Several researchers have also mapped medication errors in their papers according to this model (35, 71, 72).

1.5.3 Non-linear complex models

Modern complex systems have humans and advanced technology embedded within complex social structures (e.g. legislation or political and economic elements) forming complex socio-technical systems. In such systemic models, interrelated components (human, technology, organization, and social aspects) have several interactions and interrelationships occurring in a nonfamiliar or unexpected manner (51). Understanding the interconnected network of factors as well as the combination of the mutually occurring interactions is essential to enable the identification of contributory factors and prevention of future events (52).

There are two main non-linear dynamical models that were introduced in the early 2000s (52). The Systems-Theoretic Accident Model and Process (STAMP) of Leveson and the Functional Resonance Accident Model (FRAM) of Hollnagel (57, 73). Hollnagel's three-dimensional model (Figure 1.6) gained more publicity and was more applied in practice as it has been suggested that Leveson's model does not link well to the current method of collecting and analyzing safety data (74).

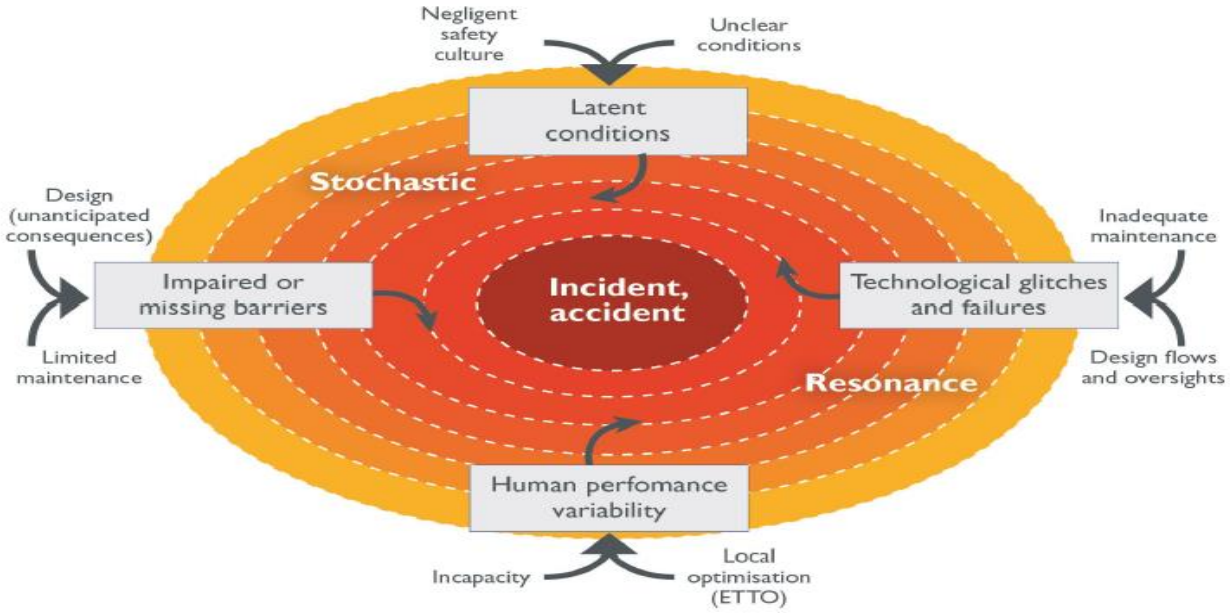

Figure 1. 6 The Functional Resonance Accident Model (Hollnagel, 2004)

These frameworks are usually utilized to describe (but not predict or explain) an incident, which could limit their utility particularly in the arena of medication errors and other patient safety incidents (57, 73, 75). Additionally, the process of the FRAM model could be time and resource consuming, which could make researchers reluctant to utilize it. Nevertheless, there is a growing interest in the FRAM model from researchers in various domains including healthcare (76, 77). To date, it has not yet been used in medication errors research.

1.6 Outpatient and ambulatory settings

The Center of Disease Control and Prevention (CDC) defines healthcare settings as “a broad array of services and places where healthcare occurs” (78). Healthcare institutes deliver services in multiple settings such as acute care settings, inpatient settings,

outpatient settings, hospice home, and long-term care facilities (78). In this section, outpatient and ambulatory settings will be discussed in detail as they are the focus of phase two of this thesis. A definition of these settings will be presented, followed by a discussion about the evolving role of outpatient and ambulatory settings in healthcare systems. The favorable outcomes as well as the challenges associated with providing care in these settings will also be highlighted in this section.

1.6.1 Definition of outpatient and ambulatory settings

Outpatient and ambulatory care are defined as the provision of any medical service by general or specialized practitioners that does not require overnight hospital stay. This includes office visits to general (i.e. primary care) or specialized (e.g. medicine, obstetrics/gynecology) clinics as well as day care units in which simple procedures are conducted or certain medications (e.g. chemotherapy) are administered (79, 80).

1.6.2 Transition from inpatient to outpatient and ambulatory settings

Three decades ago, healthcare systems began to actively transition from inpatient to outpatient medicine, whenever the patient case allows (81). This transformation could be due to the technological innovations that allowed several interventions to be performed in the outpatient context without increasing the immediate and delayed post-operative complications (82, 83). Care delivery in outpatient settings has been shown to be cost-effective as it reduces the utilization of hospital resources and the occurrence of admission-related complications (84, 85). Subsequently, this mitigates the burden on health systems.

1.6.3 The impact of delivering care in outpatient and ambulatory settings

The main goal of the outpatient setting is to ensure continuity of medical care throughout the patient life and particularly after hospital discharge (86). Continuity of care is extremely important as it is an indicator of the quality of care provided (87, 88). High-quality outpatient services have been associated with improvement in various clinical outcomes. These beneficial outcomes were persistent across multiple reports with different study designs. For instance, better management of chronic conditions, such as diabetes, hypertension, and dyslipidemia, was noted in patients attending outpatient clinics that maintain continuity of care (89). These findings are based on data from 1400 adults with diabetes who took place in the Third National Health and Nutrition Examination Survey (NHANES III). In this survey, data was collected in two phases and stratified according to the level of continuity of care.

A critical review of 40 studies showed that outpatient settings that maintain interpersonal continuity of care, significantly improved 51 out of 81 care outcomes evaluated (87). The narrative synthesis showed favorable findings mainly related to improvement in preventive services and reduction in hospital admission; however serios methodological concerns were identified in the included studies (87). Outpatient services were also associated with significant reduction in 30-day hospital readmission in a large-scale (55,378 adult patients) retrospective observational cohort study conducted in the US. The study also suggest that this outcome is more predominant when the timing of the follow-up is early and when there is high risk of readmission (90). Similarly, two nationwide observational cohort studies from France and Korea showed that outpatient settings were

associated with a significant reduction in all-cause mortality (91, 92). The study conducted in France reported that the higher the continuity the lower the mortality rate (91). The study conducted in Korea also demonstrated a significant reduction in cardiovascular mortality, cardiovascular events, and healthcare expenditures (92).

1.6.4 Challenges in outpatient settings

Work overload, inappropriate educational environment, limited number of clinically competent professional role models, and inadequate supervision models have been described as the most common problems that could negatively impact outpatient medical education (93, 94). Practitioner-related issues have also been reported as a challenge for implementing a high-quality outpatient care. One of the main themes that emerged under this domain is miscommunication among clinicians, which imposes discontinuity and consequently threatens all the favorable outcomes discussed in section 1.6.3 (95).

Previous studies suggest that medical errors (particularly diagnostic and medication errors) have been increasingly reported in outpatient as compared to inpatient settings (96-98). A report published in 2021 by the NHS showed that more than 70% of the 66 million clinically significant medication errors were in primary care settings (41). Whilst there is no systematic synthesis of the factors contributing to medication errors in these settings, some studies have looked into the factors contributing to diagnostic errors (86, 95, 99, 100). These studies suggested that contributory factors to diagnostic errors stemmed partly from the organization level. Examples include inefficiencies in diagnostic investigations and referral processes, inadequate electronic medical record systems that

lack necessary elements (e.g. medication lists, laboratory results), and low technology implementation (e.g. handwritten prescriptions) (95, 99, 100).

1.7 Study rational and significance

1.7.1 Phase one: an umbrella review of systematic reviews on contributory factors to medication errors in healthcare settings

Medication errors are common and costly patient safety incidents across various healthcare settings (section 1.3). They create a major health concern as they are associated with detrimental consequences on patients, families, societies, and health systems (section 1.4). Hence, ensuring medication safety have been declared as an international priority by the WHO (101).

Multiple systematic reviews have investigated the factors contributing to medication errors which necessitate the aggregation and filtration of the large body of literature. Thus, it is imperative to conduct an umbrella review that collate, systematically synthesize, and critically appraise the evidence from the existing reviews. The purpose is to identify common contributory factors across diverse healthcare settings. This synthesis of contributory factors is expected to guide researchers, healthcare professionals, and policy makers in prioritizing the factors to be addressed and designing tailored interventions.

1.7.2 Phase two: prevalence, nature, contributing factors, and interventions to mitigate medication errors in outpatient and ambulatory settings: a systematic review

Since the release of “To Err Is Human” landmark report by the IOM in 1999, tremendous global efforts have been dedicated to optimizing the care provided to patients by minimizing medication errors. Medication errors and its sequalae (discussed in section 1.4) represents a public concern due to their dire health implications. These implications pose serious challenges on patient safety which is a core component of any healthcare system (102). Therefore, many researchers focused on investigating the epidemiology and contributory factors to medication errors to enable the implementation of effective mitigation strategies (3).

Outpatient care is a fundamental part of all healthcare systems as it streamlines clinical processes without hospital admission and beds use. The utilization of these services exponentially increased over the years. The CDC estimated 860.4 million visits to the ambulatory settings in one year corresponding to 267.1 visits per 100 persons (103). Advantages of high-quality outpatient services are a legion, but they include enhance patient satisfaction, improve management of comorbidities, reduce emergency department visits, decrease hospitalization, and alleviate healthcare costs (87-92, 104, 105).

Several systematic reviews and meta-analyses have explored medication errors in diverse inpatient settings. Some of these reviews focused on a particular type of medication errors (e.g. prescribing errors), a certain cohort of patients (e.g. heart failure

patients), or a prespecified geographical region (72, 106, 107). Prevalence, nature, and contributory factors to medication errors in outpatient settings on the other hand have been less rigorously examined.

A review of the literature yielded a limited number of systematic reviews investigating medication errors in outpatient settings. Some of these reviews focused on a subset of medication errors such as dispensing errors (108) or preventable ADE (defined as an ADE attributable to a medication error) (109). Other reviews focused on the community care context (110), long-term care facilities (111), and community settings upon discharge (112). The last identified systematic review was Gulf Cooperation Council (GCC)-based and it included a variety of settings, of which ten studies reported outcomes from outpatient settings (113).

As evident from the literature review, there remains a dearth of reviews covering different aspects of medication errors in these settings. Referring to what actually constitutes outpatient settings (section 1.5), there is a lack of a systematic review that explore medication errors in outpatient clinics and ambulatory settings. Finding from such review will enable estimating the prevalence of medication errors and understanding the nature and factors contributing to these errors. This will facilitate the development of evidence-based prevention measures that target the exact contributory factors. Eventually, this will reduce the magnitude of medication errors in outpatient and ambulatory settings and improve patient safety.

1.8 Aim and objectives

1.8.1 Overall aim of the thesis

The aim of this thesis was a) to systematically evaluate contributory factors to medication errors in healthcare settings in terms of the nature of these factors; methodologies and theories used to classify them; and terminologies and definitions used to describe them, b) to synthesize the literature on the prevalence, nature, contributory factors, and interventions to minimize medication errors in outpatient and ambulatory settings (Figure 1.7). Findings from phase one (umbrella review) of this thesis will inform the content and methodological approaches of the second phase (systematic review).

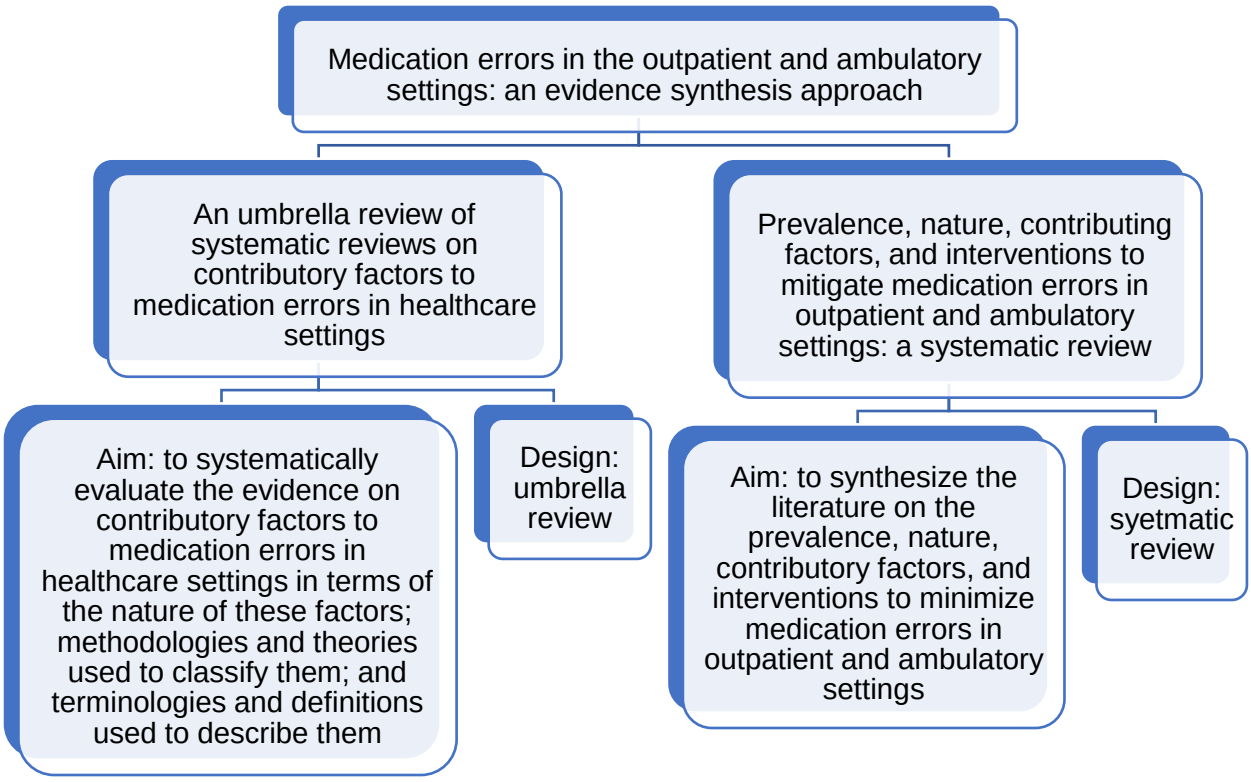

Figure 1. 7 The overall aim of the thesis

1.8.2 Phase one: an umbrella review of systematic reviews on contributory factors to medication errors in healthcare settings

Aim: to systematically evaluate contributory factors to medication errors in healthcare settings in terms of the nature of these factors; methodologies and theories used to classify them; and terminologies and definitions used to describe them

Objectives:

1- To systematically synthesize the terms and definitions of contributory factors adopted by the published systematic reviews
2- To systematically synthesize and assess the rigor of the methodologies, theories, models, and frameworks adopted by published systematic reviews to identify and classify contributory factors to medication errors
3- To systematically synthesize the contributory factors to medication errors reported by systematic reviews
4- To systematically synthesize the terms and definition of medication errors adopted by published systematic reviews
5- To systematically synthesize the interventions aimed to mitigate contributory factors linked to medication errors

1.8.3 Phase two: prevalence, nature, contributing factors, and interventions to mitigate medication errors in outpatient and ambulatory settings: a systematic review

Aim: to systematically evaluate the prevalence, nature, contributory factors, and interventions to minimize medication errors in outpatient and ambulatory settings

Objectives:

1- To estimate the prevalence of medication errors in outpatient and ambulatory settings
2- To classify medication errors in outpatient and ambulatory settings according to
    a. stage in the medication use process
    b. incident types
    c. severity
3- To identify, synthesize, and classify contributary factors to medication error in outpatient and ambulatory settings
4- To systematically review the interventions aimed at mitigation of medication error in outpatient and ambulatory settings

Chapter 2: Methodology

This chapter will focus on the methodological aspects related to evidence reviews. The most common types of reviews will be presented in the first section, followed by an overview of the reporting guidelines as well as the key stages and best practices for conducting reviews. The discussion will be focused on systematic reviews and umbrella reviews throughout, as they are of interest to the current thesis.

2.1 Typology of reviews

The expansion of evidence-based practice (EBP) has led to a plethora of published research aiming to answer the same question (114). Hence, there was a need to collate this evidence by conducting reviews. A variety of review methodologies (around 14 types) have been documented in the scientific literature, with each having its unique characteristics to serve a different purpose (114). It is crucial to distinguish between these types to be able to choose the methodology that best answers the research question. Table 2.1 summarize the features of the most commonly used reviews.

Table 2. 1 Features of selected types of reviews

	Narrative review	Systematic review	Scoping review	Umbrella review
Hypothesis	Broad overview	Focused research question	Broad research question	Focused research question
Methods	Not predefined	Predefined, protocol-based	Predefined protocol-based (iterative approach)	Predefined, protocol-based
Quality assessment	May or may not be include	Required and may determine inclusion	No formal quality assessment	Required and may determine inclusion
Purpose	Provide a summary or overview of a topic	Sum up the best available research on a specific question	Map the literature on a topic	Summarize the evidence from multiple research syntheses
Outcome	Descriptive overview	Synthesis of evidence (meta-analysis includes statistical analysis)	Descriptive overview	Synthesis of systematic reviews

2.1.1 Narrative review

Narrative reviews are considered a succinct summary of some of the available evidence that can be conducted by as low as one researcher (115). Unlike systematic reviews, it is not a prerequisite to have a prespecified protocol, quality assessment, or to include all published studies. Therefore, it is considered the lowest level of rigor amongst other reviews and researchers prefer the evidence from systematic reviews over it (114, 116).

2.1.2 Systematic review with or without meta-analysis

Cochrane library defines a systematic review as “a review that attempts to identify, appraise and synthesize all the empirical evidence that meets pre-specified eligibility

criteria to answer a specific research question" (117). It includes a thorough search of the literature to compile all existing empirical evidence on a specific research question to formulate pooled findings (115).

For reviews that have a quantitative outcome of interest, when the research question is very-well articulated and sufficiently homogeneous studies are included, a meta-analysis can be executed as a last step. A meta-analysis, is a statistical technique to combine the findings of quantitative studies to increase the statistical power (114). For reviews that aim to integrate qualitative studies, a meta-synthesis (also known as qualitative meta-analysis) can be conducted (118). Any of the methods for the synthesis of qualitative research could be used such as thematic analysis or meta-regression to identify key themes, concepts, or theories that offer a more powerful explanations of the phenomenon of interest (119).

When possible, systematic reviews are recommended because they are classified as the highest level of evidence (Figure 2.1) (116, 120).

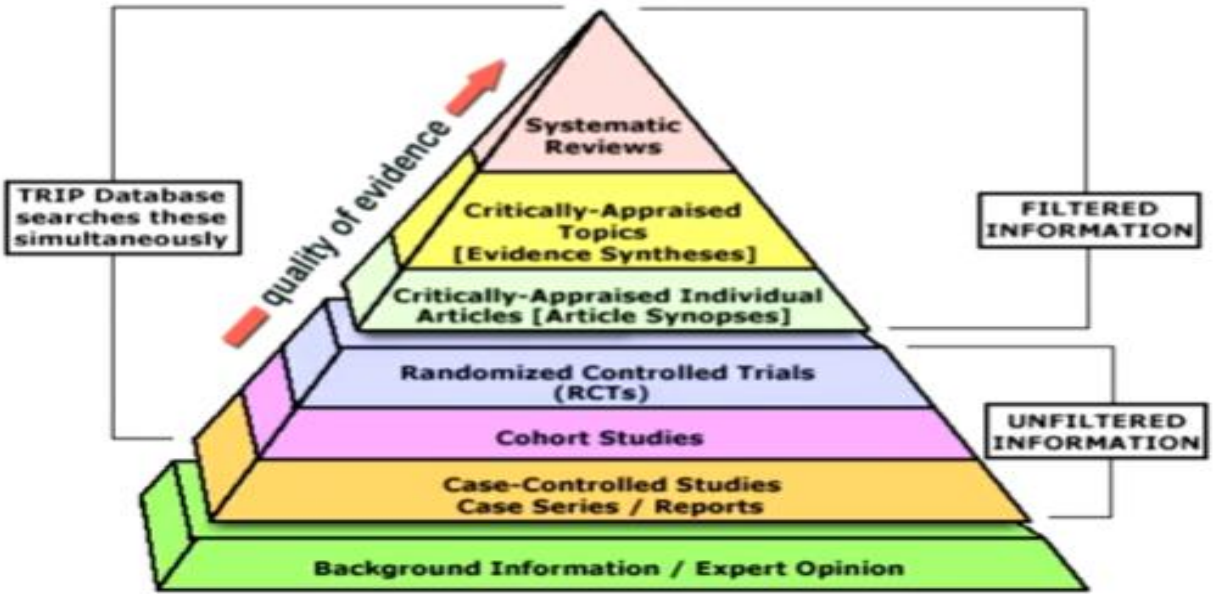

Figure 2. 1 Hierarchy of evidence (Sackett et al., 2000)

2.1.3 Scoping review

A scoping review can be defined as “a preliminary assessment of potential size and scope of available research literature. Aims to identify nature and extent of research evidence (usually including ongoing research)” (114). Scoping reviews are set up to map the body of literature on a broad topic area to assess the extent and scope of evidence and subsequently identify the gaps in research and areas where there is sufficient literature to undertake a more precise systematic review (114, 115, 121).

Scoping reviews are considered a valid alternative to systematic reviews when more specific questions are not clear yet. Although scoping reviews have less rigor compared to systematic reviews, they are still recognized as a structured synthesis that requires preliminary search strategy (122). Unlike systematic reviews, an iterative approach to

methods is allowed and quality assessment is not required (115). Unlike narrative reviews, results are usually presented in tabular format (122).

2.1.4 Umbrella review

Syntheses of available systematic reviews enables collation and comparison of findings from different reviews (123). An umbrella review can be defined as “a review compiling evidence from multiple reviews into one accessible and usable document. It focuses on broad condition or problem for which there are competing interventions and highlights reviews that address these interventions and their results” (114). Umbrella reviews could enhance the access to targeted information and inform healthcare decision-making process (114, 124). This placed umbrella review, also called overview of reviews, at the top of the hierarchy of secondary research (Figure 2.2) (125). It is a requirement for umbrella reviews to encompass a priori protocol and critical appraisal of included systematic reviews (123).

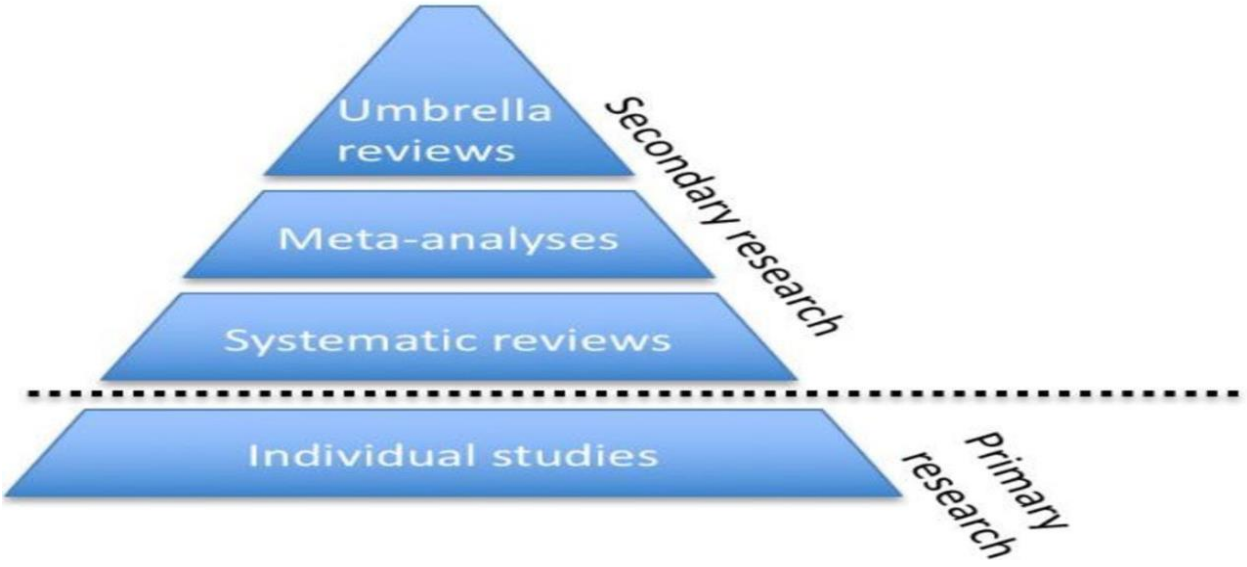

Figure 2. 2 Hierarchy of secondary research (Fusar-Poli et al., 2018)

Inconsistency in the terms used to refer to syntheses of systematic reviews has been highlighted in the literature. A study revealed that 116 terms have been used to describe syntheses of systematic reviews such as overview, overview of reviews, overview of systematic reviews, umbrella review, metareview, systematic review of reviews, review of systematic reviews among others (126). Whilst a previous descriptive analysis (2012) illustrated that “overview of reviews” is the most common term identified from the literature, a more recent report (2016) showed that “overview of systematic review” is more frequently used (126, 127).

A great degree of ambiguity still underpins the nomenclature of syntheses of systematic reviews. Most researchers have used the different terms interchangeably; however some researchers suggested that minor differences could exist (117, 128). For example, few researchers view the term “overview” as the broader term, whereas they use “umbrella review” for overviews that allow the inclusion of primary research and “overview of reviews” for overviews that explicitly incorporate systematic reviews (129-131). Nonetheless, there is a lack of consensus regarding these terminologies and most researchers use the terms interchangeably.

2.1.5 Other types of reviews

In addition to the review types described above, there are other, less common, types that have been mentioned in the literature. This includes rapid reviews, critical reviews, state-of-the-art reviews, and mapping reviews amongst others (114, 115). Each of these reviews has its distinguished applications.

2.2 Guidelines for reporting selected types of reviews

A reporting guideline was defined by Moher et al (2010) as “a checklist, flow diagram, or explicit text to guide authors in reporting a specific type of research, developed using explicit methodology” (132).

Several guidelines have been developed to direct researchers while conducting a review and to set minimum required standards for good quality reviews that generate reliable evidence. In the upcoming sections, the most common guidelines for reporting systematic reviews and umbrella reviews are highlighted. The focus was on these two types of reviews as they are of interest to the current thesis.

2.2.1 Guidelines for reporting systematic reviews

2.2.1.1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)

PRISMA checklist (last updated in 2020) is a tool to ensure the rigorous and transparent reporting of systematic reviews and meta-analyses outcomes (133). It has been extensively utilized in the literature and it is the guidelines used to report the results of phase two of this thesis (32, 33, 72, 102, 134, 135). This checklist comprises seven categories (title, abstract, introduction, methods, results, discussion, and other information) and 27 items, with some items having sub-items.

Several extensions have been developed to cover other types and aspects of reviews such as scoping reviews (PRISMA-ScR), network meta-analyses, protocols (PRISMA-P), or literature searching (PRISMA-S) (136-139).

2.2.1.2 Cochrane guideline

Cochrane has two handbooks, one for systematic reviews of interventions and the other for diagnostic test accuracy (117, 140). These guidelines were originally established to guide authors while writing Cochrane systematic reviews; however authors of standard systematic reviews have also used these guidelines (32, 141).

The handbook of interventions (last updated in 2011) is one of the tools recommended for drug safety research (142). It consists of four parts, in which the second part consists of 15 sections and discusses the core methods from starting a review to interpreting results. In brief, this handbook covers all aspects of a systematic review including planning, search strategy, studies selection, data extraction and collection, quality assessment, statistical analysis and data synthesis, and results interpretation (117).

2.2.1.3 Joanna Briggs Institute (JBI) manual for evidence synthesis: JBI systematic reviews

Every year the JBI (based in Australia) publishes a manual to support researchers who are conducting a systematic review according to the JBI methodology (143). In their manual, they seek to provide guidance for all types of systematic reviews (e.g. systematic review of effectiveness, or systematic review of qualitative evidence). The manual for JBI systematic reviews endorses the PRISMA instrument. Additionally, they included sections for planning, registering, and publishing a review (143). For registration, they recommended PROSPERO, the international prospective register of systematic reviews (144).

For all other types of systematic reviews, they developed their own detailed guidance in separate chapters. The JBI also produced manuals for other types of reviews, such as umbrella reviews and scoping reviews (123, 143).

2.2.1.4 Standards for systematic reviews by the Institute of Medicine (IOM)

The IOM published 21 recommendations in 2011 for undertaking high-quality systematic reviews (145). It addresses all the steps required in the process, starting from locating and assessing eligible studies to quality assessment and findings synthesis (including meta-analysis). It also has a chapter dedicated for producing a final report. It provides a general layout for sections recommended to be included in each systematic review report, which could also be beneficial for journals. In this outline, in addition to all sections covered by previous tools, they recommend incorporation of a summary in lay language for the public, (145).

2.2.1.5 Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in healthcare

In 2009, the CRD developed a detailed guideline for conducting and presenting systematic reviews. In addition to the general guidance, this organization provides specific recommendations to each research field (e.g. health intervention or adverse effects). For instance, they specify the preferred databases or risk of bias tools for each field (146). This guideline covers all the criteria described in previous tools as well as archiving the review and disseminating the findings (146). It is also recognized as one of the most commonly used guidelines for reporting systematic reviews focusing on drug safety (142).

2.2.1.6 Meta-analysis Of Observational Studies in Epidemiology (MOOSE)

The MOOSE group initially proposed its checklist in 2000 in a paper published in JAMA journal (147). The tool comprised 35 items under 6 broad categories (background, search strategy, methods, results, discussion, and conclusion). The utility of this instrument is specific to observational studies in epidemiology research; however it has also been used for systematic reviews focusing on this study design (148-151).

2.2.1.7 Methods guide for effectiveness and comparative effectiveness reviews

This guide was published by the Agency for Healthcare Research and Quality (AHRQ) in 2008 and updated in 2014. It is specific to systematic reviews of effectiveness, comparative effectiveness, and comparative harms of different healthcare interventions (152). Although it is a thorough and detailed tool, it was originally designed for the Effective Health Care Program (in the US) and was found to be very lengthy (consists of 17 book chapters, with no abridged checklist) which might limit its usability (142).

2.2.2 Guidelines for reporting umbrella reviews

2.2.2.1 Joanna Briggs Institute (JBI) manual for evidence synthesis: umbrella reviews

The JBI publishes a manual every year for different types of reviews with one chapter focusing on umbrella reviews (143). In this chapter, authors incorporated guidelines for developing umbrella review protocol as well as building the manuscript. Seven sections are presented under the JBI umbrella review approach to reporting. They cover title, authors, executive summary, main body of the report, methods, results, and summary of evidence. Each section is further divided to include all components required in the final report, forming a template for authors to follow (143).

The JBI group developed an easy-to-use 11-item checklist for critical appraisal; however they also discussed other available options (such as AMSTAR and ROBIS tools) (123, 153, 154). Moreover, they developed a generic data extraction sheet that is divided into five sections (including a comments section) and 17 items (143). They recommend presenting the results in tabular format and including a final and easily interpretable table to summarize the evidence. This final table is important as it fulfils the main goal of JBI umbrella reviews which is to provide an informative and accessible summary of the body of evidence (143).

In the first phase of this thesis, the JBI manual was used to report the findings from the umbrella review. The quality of included systematic review was assessed via the proposed 11-item checklist. Additionally, the data extraction sheet proposed in the JBI manual was adopted with modifications to suit the purpose of the current umbrella review.

2.2.2.2 Metareview Assessment of Reporting Quality (MARQ)

MARQ is one of the earliest checklists that was developed in 2012 to report finding from metareviews. This tool has 20 components to cover title, abstract, introduction, methods, results, discussion, and role of external sources (155). Although there is no sufficient explanation provided for each item and some important components are missing (e.g. registration), this instrument provides a good grounding for future tools.

2.2.2.3 Umbrella reviews: evidence synthesis with overviews of reviews and meta-epidemiologic studies

A chapter entitled “State-of-the-Art Reporting” written by Onishi and Furukawa (2016) in a book devoted solely for umbrella reviews, provided a reporting checklist for tertiary

research with focus on umbrella reviews (156). This 22-componant instrument involves title and abstract, introduction, methods, results, and discussion (156). They also provided explanation for each item. The authors recommended registration with PROSPERO (144). Additionally, they discussed a variety of quality assessment tools without formulating a specific recommendation for a preferred one (156).

2.2.2.4 Preferred reporting items for overviews of systematic reviews (PRIO-harms)

This instrument was proposed in 2018 to assist umbrella reviews' authors in reporting their findings with emphasis on balancing harms and benefits (157). In the development process they mainly relied on previously published tools, including PRISMA, PRISMA-P, and PRISMA harms (133, 139, 158). The checklist contains 27 items and 56 subitems to ensure the complete and transparent reporting of the five stages required for overviews (identification, screening, eligibility, inclusion, and separation of relevant studies) (157).

In 2019, the same group developed the first guidelines for reporting abstracts for overviews (159).

2.2.2.5 Standards for reporting of overviews of reviews and umbrella reviews (STROVI)

An abstract was presented by Posadzki P at the Cochrane Colloquium (2017); however a paper published in 2019 declared that there was no progress on this project (160).

2.2.2.6 Ten simple rules for conducting umbrella reviews

In 2018, Fusar-Poli and Radua developed ten key rules, obtained from a critical review, to note before embarking an overview (125). While this paper highlights important points, it follows a non-systematic approach, whereby it does not represent a reporting guideline.

2.2.2.7 Preferred reporting items for overviews of reviews (PRIOR)

In line with the recommendations provided by the Enhancing QUAlity and Transparency Of health Research (EQUATOR) Network, Gates et al (2022) intended to develop an evidence-based and agreement-based reporting guideline for all types of tertiary research (132, 160). The PRIOR statement and its explanation report are available as preprints (161, 162). The checklist consists of 27 items and 19 sub-items that cover all aspects involved in overviews of reviews, including title, abstract, introduction, methods, results, discussion, and other information (161). They also advised registering with PROSPERO prior to initiating the study (162).

Authors developed a PRIOR flow diagram and advised incorporating it in any overview of reviews that includes both syntheses and primary literature. They also have suggested that reporting the two types of research in separate flow diagram is acceptable (162). The PRIOR flow diagram is similar to the PRISMA flow chart but it is more specific to overviews as it covers all the stages and possible resources that could be included in an overview (161). In cases where only systematic reviews are included, PRIOR developers suggest that adapting the PRISMA flow diagram is reasonable (133, 162).

The tool sufficiently addressed the issue of overlapping between systematic reviews and primary research. Thus, they recommended defining the eligibility of overlapping reviews, describing the process of managing it, and providing a visual representation of the nature and extent of primary research overlap (162). This instrument did not recommend a particular risk of bias assessment tool; however they suggested that appraising the systematic reviews and/or the primary studies within these reviews is acceptable (162).

Unlike the JBI guidance, PRIOR guidelines allowed the inclusion of primary studies in case they were not covered by existing systematic review (143, 162).

Although the JBI instrument was primarily used to present findings from the current umbrella review, the PRIOR tool was also used for certain areas that were not covered by the former.

2.3 Key stages and best practices for conducting a review

In this section, the focus will be on systematic reviews. The focus was on this type of reviews as unlike other types of reviews, there are multiple guidelines with a reasonable level of consensus regarding the steps and best practices. To date, there are no tools that focuses on best practices in conducting an umbrella review; hence it was not feasible to have a separate section for umbrella reviews. However, most of the below discussion could be extrapolated to other systematically conducted reviews, including umbrella reviews. Nevertheless, differences could still exist to serve the purpose of each type of review.

2.3.1 Defining the research question, aim, and objectives

As in the case of other study designs, the first step is to establish a well-defined research question that follows the PICO (population, intervention, comparator, outcome) tool (163). SPIDER (sample, phenomenon of interest, design, evaluation, research type) tool has also been utilized but less commonly and mainly for qualitative and mixed-method designs (164).

The aim and objectives also should be set at the beginning. To ensure their validity, a quick search of the main databases to identify gaps in the current body of literature is

recommended (163). The purpose of this preliminary search is to ensure the appropriateness of the potential research question. Since reviews are based on previously published articles, it is required to confirm that the topic of interest has been addressed by primary research to guarantee that a sufficient number of studies will be included in the review (143). It also is essential to avoid duplicating others work, thereby screening the literature and PROSPERO registry for published or ongoing similar reviews is mandated (143, 144).

2.3.2 Developing eligibility criteria

Inclusion criteria should be tailored to the research question; hence it is logical to follow the PICO elements and, if needed, it can be combined with the study design and timeframe (163, 164). Exclusion criteria usually includes unavailable full text, or conference proceedings (i.e. abstract-only papers) (164). However, criteria specific to the review domain could also be incorporated.

2.3.3 Search strategy

The search strategy should be comprehensive and encompasses sufficient details about the data acquisition process to ensure reproducibility (165). It should incorporate the databases (e.g. Medline) and search engines (e.g. Google Scholar). A minimum of three databases is required for high-quality systematic review according to some quality assessment tools (e.g. AMSTAR 2 tool) (129, 154).

In addition, search terms should be explicitly stated. This consist of keywords and subject indexing such as Medical Subject Headings (MeSH) terms, Embase Subject Headings (Emtree), or any alternative terms as appropriate to the database. Boolean operators

(ADJ#, AND, OR, NOT or AND NOT) utilized to combine search phrases and truncation should also be mentioned (164). If any limits are utilized, they should be stated clearly in the search strategy (133).

Grey literature (unpublished records such as government reports or thesis) is also an important element of the search strategy (166). The AMSTAR 2 checklist considers grey literature as part of the comprehensive search strategy that should be followed where appropriate (154).

2.3.4 Designing data extraction sheet

The method of developing the data extraction sheet should be recorded (e.g. by consensus or by adapting a previously published tool). If the research team developed the data extraction sheet, then piloting on a sample of the included studies should take place (163). Authors should also report the items that will be abstracted from included articles.

This step concludes the protocol. Some researchers suggests that steps described in sections 2.3.2, 2.3.3, and 2.3.4 could be conducted concomitantly (163).

2.3.5 Registration

The finalized protocol should be registered with PROSPERO (144). This is important as it will inform other researchers that this research in underway to evade duplication and wasting money, resources, and efforts (143).

2.3.6 Searching databases, exporting hits to a reference manager, and removing duplicates

Investigators could start their systematic review even before PROSPERO approves the protocol (144). First, they should run the search on all bibliographic databases and import the titles and abstracts to a reference manager, such as EndNote, Mendeley, Rayyan Qatar Computing Research Institute (QCRI), or any other software (164, 167). Second, on that reference manager, duplicates should be removed (163).

The number of articles identified from each database/search engine and the total number before and after deleting duplicates should be recorded and presented, preferably using the PRISMA flow diagram (133).

2.3.7 Titles and abstracts screening

The eligible citations should be retrieved to Excel, QCRI, or any similar software to conduct the titles and abstracts screening and record the outcomes. This stage should be done by two independent reviewers. Any discrepancies should be resolved by either a discussion between the two reviewers or by involving a third reviewer (163). After this stage, a final list of articles eligible for full-text screening should be generated and agreed upon.

2.3.8 Full text screening

This stage usually needs to be done on an Excel spreadsheet. All articles included in the final list should be downloaded and added to the Excel sheet. Similar to the title/abstract screening stage, full-text screening should be performed by two independent reviewers and consensus should be sought through one of the discussed methods (163).

PRISMA flow chart should be utilized throughout the screening stages to record the numbers of remaining articles after each stage (133). It is important to include the reasons for all articles excluded during the full-text screening. Reference lists of included articles should be searched in this stage. Any possibly eligible articles that were not identified through the initial search, should be manually added to the final list and screened (164).

2.3.9 Seeking expert opinion

Identify experts in the domain of interest could be done by reviewing the authors lists for articles eligible for inclusion after the full text screening. Then, they can be contacted to inquire about ongoing research and suggested references (117). Before including any of the suggested articles, authors should make sure that they are not duplicates and the PRISMA flow diagram should be updated and finalized after this stage (163).

2.3.10 Data extraction and quality assessment

Data extraction process should follow the data extraction form developed a priori (164). Similarly, risk of bias assessment should be done via a validated tool that are suitable to the study design. The critical appraisal tool should be selected in advance, as part of the protocol, to accommodate for all included or expected study designs (165). Both phases should be conducted by two reviewers independently.

2.3.11 Data synthesis with or without meta-analysis

This stage entails assimilating and summarizing the findings obtained after data extraction. All systematic reviews incorporate a narrative summary of their findings. This could be followed by a quantitative synthesis via a meta-analysis or a qualitative synthesis via meta-synthesis (119, 165).

The descriptive synthesis depends mainly on words to synthesize the results. A brief tabular illustration is recommended to summarize the outcomes in an easy and accessible format (168). Sometimes, it might involve some numerical component (163). For example, sociodemographic parameters could be summarized as median (IQR: interquartile range) or mean (±SD: standard deviation) as appropriate. Categorical variables could be summarized as numbers (%).

2.4 Chapter conclusion

In this chapter, the most common types of reviews were presented, followed by a detailed discussion of the reporting guidelines and the best practices for reporting and conducting systematic reviews and umbrella reviews. Systematic reviews offer researchers and practitioners with the highest level of evidence that include primary research, while umbrella reviews offer the highest level of evidence that include secondary research.

The researcher (LN) was able to gain familiarity with key guidelines in relation to the conduct and reporting of reviews. It allowed the researchers to consider and compare different tools and subsequently adopt the tools that are best suited for this thesis. It also allowed the researchers to follow best practices during the conduct of the current thesis which ensures that the work presented in this thesis is of high methodological quality.

Chapter 3: an umbrella review of systematic reviews on contributory factors to medication errors in healthcare settings

This chapter will provide an introduction to the concept of contributory factors to medication error. This is followed with a detailed description of the methods adopted in the current umbrella review. The findings are presented in the results section. The findings are then thoroughly discussed, in context of other research, in the discussion section. The discussion also demonstrated directions for future researchers who aim to investigate contributory factors in relation to optimizing the design and robustness of their research. Our synthesis of contributory factors to medication errors could also inform the content of future interventions that target the exact deficiencies across the healthcare system.

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3.1 Introduction

Medication errors are prevalent events that take place across the entire spectrum of the medication use process (4, 169). The National Coordinating Council for Medication Error Reporting and Prevention (NCCMERP) in the United States (US) defines a medication error as “any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer” (10).

Consequences of medication errors can range from no or mild harm to severe harm and death (8, 41). For instance, in England, 237.3 million medication errors occur every year, with 66 million considered potentially harmful (41). The same report noted that medication errors caused 712 deaths and contributed to more than 1700 deaths in one year (41). The World Health Organization (WHO) estimated the global impact of medication errors to be approximately $42 billion annually (39). Additionally, medication errors have a deleterious psychological impact on patients, families, and health practitioners (47, 48).

Evidence suggests that up to 60% of medication errors are under-reported (170, 171). The practice of detecting and reporting medication errors by healthcare providers, as well as investigating and analyzing such errors through rigorous research, is imperative to promote patient safety (172).

A myriad of potential strategies has been suggested to decrease medication errors and improve patient outcomes, including pharmacist-led interventions, educational interventions, technology-driven interventions, and multidisciplinary team

implementation. While a number of studies have demonstrated reduction in the incidence of errors due to intervention, negative or no effects have also been reported (32, 134, 135, 173-175). In addition, there is a dearth of literature that describe the rationale and theoretical basis for intervention development targeting relevant contributory factors (102, 176).

Several primary studies and systematic reviews have explored factors contributing to medication errors. Given the plethora of systematic reviews investigating contributory factors to medication errors, there is a need to identify, critically appraise, and synthesize these factors via an umbrella review. This will enhance access to high-quality evidence; provide recommendations to improve the robustness of future work; increase the understanding of contributory factors; and inform decision-making regarding the development of evidence-based and holistic interventions to reduce medication errors.

This study aimed to undertake an umbrella review of systematic reviews on contributory factors to medication errors in diverse healthcare settings in terms of the nature of these factors; methodologies and theories used to identify and classify these factors; and terminologies and definitions used to describe them.

3.2 Methods

3.2.1 Methodology reporting and registration

This umbrella review followed the recommendations provided by the Joanna Briggs Institute (JBI) reporting methodology manual and the Preferred Reporting Items for Overviews of Reviews (PRIOR) reporting guidelines-preprint (123, 161, 162). The review

protocol is available in PROSPERO, the international prospective register of systematic reviews, under the registration number CRD42022321425 (Appendix 1) (177).

3.2.2 Eligibility criteria

Reviews were considered for inclusion if they met the following criteria:

Domain:

Systematic reviews using different causation terms (e.g. contributory factors, causes, risks) were included in the current umbrella review. There is no unified definition of contributory factors to medication errors thereby the current umbrella review worked with the definitions provided by the included systematic reviews. For the purpose of this review, the NCCMERP definition of medication errors was adapted (refer to section 1.1). Definitions of medication errors employed by each systematic review were also captured.

Participants:

No restriction on age, gender, or clinical specialty was imposed.

Intervention(s):

This review is not assessing a particular intervention and its impact on medication errors; thus the presence of a certain intervention/exposure is not a requirement for inclusion.

Comparator(s):

Not applicable.

Outcomes:

Studies will only be included if they reported on contributory factors to medication errors. Outcomes of interest include:

1- Terms, definitions, methodologies, theories, models, and frameworks adopted by systematic reviews to identify and classify contributory factors to medication errors
2- Classifications and the exact contributory factors to medication errors as reported by systematic reviews
3- The definition of medication errors adopted by systematic reviews and the terms used to describe medication errors
4- The interventions aimed at mitigating the identified contributory factors to medication errors that have been described in existing systematic reviews

Type of studies:

Systematic reviews with or without meta-analysis.

Period:

No restriction on the date of publication.

Exclusion criteria: (1) non-English language publications; (2) papers focusing on adverse drug events (ADEs, i.e. harm experienced by a patient as a result of exposure to a medication. ADEs encompassing a wide range of incidents, such as adverse drug reactions and medication errors) (178) with lack of clear relevance to medication errors; (3) narrative reviews, scoping reviews, or any other type of review.

3.2.3 Data sources and search strategy

Searches were undertaken on four electronic databases and search engines from their inception to March 29, 2022:

- Medline: the National Library of Medicine's (NLM) bibliographic database of the US that covers articles since 1966. It indexes over 5,200 journals and 29 million references worldwide. The thesaurus used by Medline is called Medical Subject Headings (MeSH) (179, 180).
- Embase: a biomedical bibliographic database that is published by Elsevier and covers articles published from 1947 to present. It contains around 10 million titles that are not covered by Medline and 2900 unique journals. Embase Subject Headings (Emtree) indexing is utilized by Embase (181). A recent study showed that combining Medline and Embase increases the coverage rate of studies to 88.0% (182).
- Cumulative Index to Nursing and Allied Health Literature (CINAHL): a bibliographic database that indexes 3604 journals, including the premier nursing and allied health journals. Similar to Medline, MeSH terms are used in CINAHL (183). Two studies showed that searching CINAHL in addition to any combination of general databases yields unique citations related to nursing and 17 allied health disciplines as well as qualitative research (184, 185).
- Google Scholar (first 500 records): a search engine that includes both academic and grey literature. Its use in evidence syntheses has been recommended as it

provides a useful source of grey literature, which is one of the requirements for high-quality systematic reviews (186).

The process also included manual searches of the bibliographies of papers retrieved through the database search.

Search terms related to categories A (related to medication errors), and B (related to systematic reviews) were combined with Boolean operators (AND/OR). We did not incorporate terms related to contributory factors to avoid missing any relevant reviews as variation in the terminologies was expected. The result of this search was limited to 'English language', 'Human species', 'Systematic reviews', and 'Meta-analysis' as applicable to each database (Table 3.1). We limited the search to English only publications as it is the language spoken by all members of the research team. The detailed search strategy, MeSH, and other search terms were modified to suit each information source (Appendix 2).

Table 3. 1 Search terms for phase one (umbrella review)

Category	Search terms
Medication errors	Medication error [MeSH] OR ((medication* OR transcrib* OR prescrib* OR dispens* OR administ*) adj3 (incident* OR mistake* OR error*))
Systematic review	Systematic review* OR Meta-analysis

3.2.4 Study selection

All retrieved articles were exported to EndNote 20® (2021 Clarivate), duplicates removed, and the remaining papers imported to Rayyan Qatar Computing Research Institute (QCRI) software for the titles and abstracts screening (167). This was followed by full-text

screening via Microsoft Excel. The two-phase screening process was conducted by two independent reviewers (LN, RAA) and discrepancies were resolved through a consensus discussion with a third reviewer (VP).

3.2.5 Data extraction

Data were extracted by one reviewer (LN) and verified by a second reviewer (VP) by adopting and modifying on a standardized tool available in the JBI Reviewers' Manual (123). The standardized data extraction sheet was modified through discussion between two reviewers (LN, VP) to fulfil the objectives of the current umbrella review (Appendix 3), then piloted on five randomly chosen included studies. The data extraction form included elements pertaining to the below categories:

- Characteristics of included systematic reviews: authors, year of publication, study design, context (e.g. geographical location, settings, pharmacological category), number of included primary studies, and eligibility criteria
- Search details: databases searched, other resources, search timeframe, limits, terms specific to contributory factors (if any)
- Quality appraisal (methodological quality, quality of evidence) of primary studies included in the selected systematic reviews as reported by authors
    - For meta-analyses: publication bias (e.g. funnel plot, statistical test) and missing primary studies, analyses, or results (e.g. ROB-ME)
    - If systematic review authors did not assess for the methodological quality, publication or reporting biases, this was noted with authors' rationale if provided

- Contributory factors: terminology, definition (of contributory factors or sub-classification), classifications, reported contributory factors, methodologies, theories, models, and frameworks to identify and classify contributory factors
- Medication errors: terminology, definition (of medication errors or sub-classification), methodologies for classification of medication errors, and the sub-classes
- Interventions (if any): interventions recommended, characteristics of the interventions, delivery provider, theories/models/frameworks to develop the interventions, and outcome of the interventions

3.2.6 Quality assessment

The methodological robustness of included systematic reviews was assessed by one reviewer (LN) and verified by a second one (VP) utilizing the JBI 11-item tool for critical appraisal (123). The items are: (1) is the review question clearly and explicitly stated? (2) were the inclusion criteria appropriate for the review question? (3) was the search strategy appropriate? (4) were the sources and resources used to search for studies adequate? (5) were the criteria for appraising studies appropriate? (6) was critical appraisal conducted by two or more reviewers independently? (7) were there methods to minimize errors in data extraction? (8) were the methods used to combine studies appropriate? (9) was the likelihood of publication bias assessed? (10) were recommendations for policy and/or practice supported by the reported data? (11) were the specific directives for new research appropriate?

This instrument does not assign an overall score to the adjudicated studies; hence a narrative description of each criterion will be provided. Reviews were not eliminated based on their quality as one of the outcomes of this umbrella review is to assess the methodological approaches.

3.2.7 Data synthesis

Given the outcomes of interest are qualitative, statistical pooling in meta-analysis was not appropriate. Synthesis of findings was undertaken using a narrative approach. Narrative synthesis can be defined as “an approach to the systematic review and synthesis of findings from multiple studies that relies primarily on the use of words and texts to summarize and explain the findings of the synthesis” (187). Findings are presented in textual form and summary tables. Overlap between included systematic reviews was not assessed, as one of the objectives of this review is to assess the methodological quality of existing systematic reviews.

3.3 Results

3.3.1 Study selection

A total of 1252 citations were identified from the database searching and reference screening. Following duplicate removal, the remaining 853 articles were screened according to title and abstract (Figure 3.1). Twenty-seven systematic reviews were included in the final synthesis. The reasons for exclusion are listed in appendix 7 (Table 1). The most frequent reason for exclusion at the full text screening stage was the lack of investigation into contributory factors to medication errors.

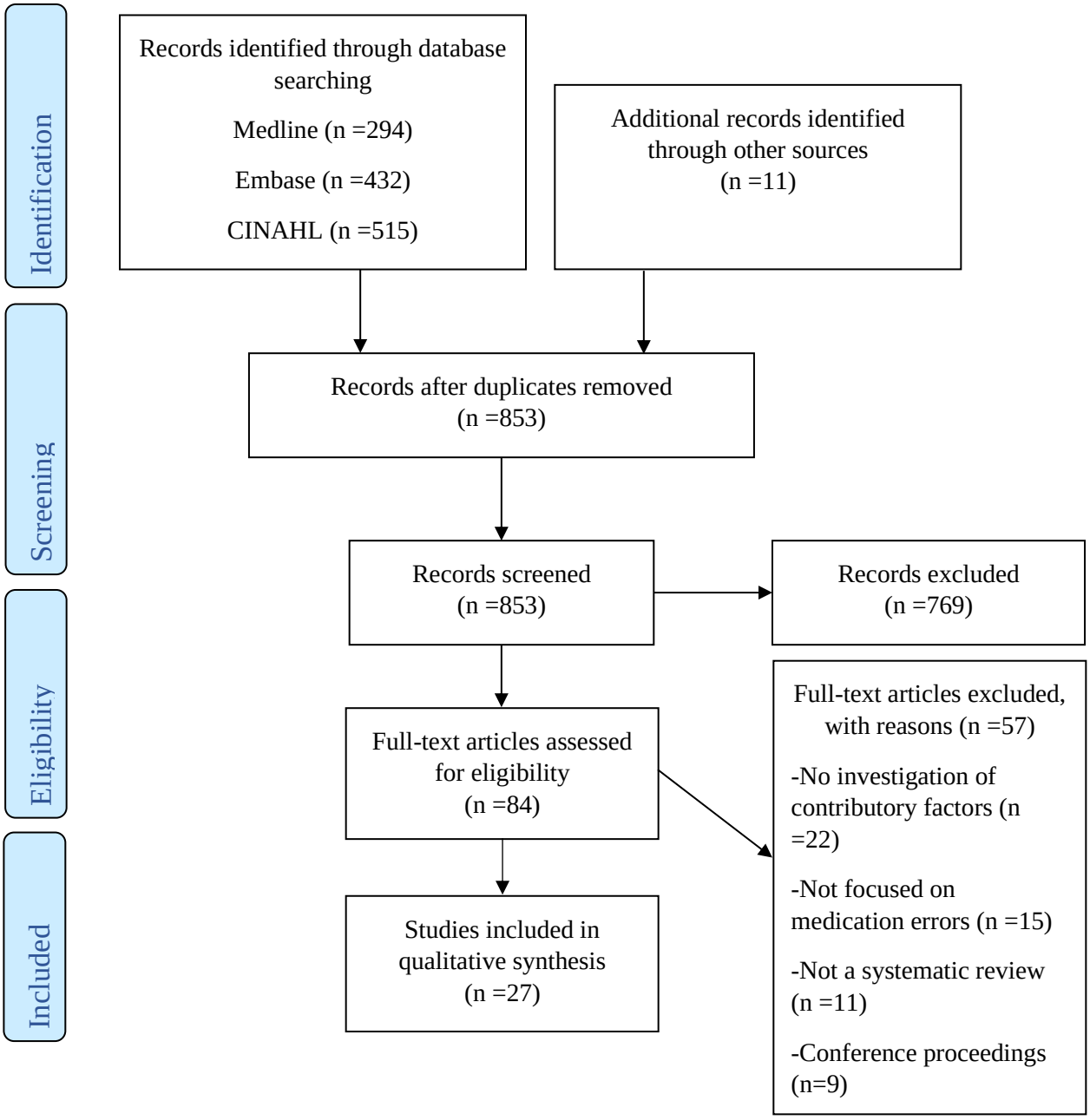

Figure 3. 1 PRISMA flow diagram of the review selection process for phase one (umbrella review)

3.3.2 Characteristics of included reviews

Table 3.2 summarizes the characteristics of the included systematic reviews. The majority were published in the last 10 years, except for one each in 2007 (188), 2009 (189), and 2010 (190). It is noteworthy that the context of included reviews was not always the study setting. For example, in some cases it was a certain geographical location or route of administration. Descriptions of study contexts are reported in table 2 and further described in this section. Of the 27 reviews, 16 focused on specific populations/settings such as community-dwelling adults (102, 111, 191, 192), home care setting (193, 194), neonatal intensive care setting (188, 195), inpatient setting (189, 196), pediatrics (197), elderly (198), hematopoietic stem cell transplantation patients (199), mental health patients (200), perioperative setting (201), or acute care setting (190).

Six reviews focused on geographical location of the Middle East (72, 202), Iran (203, 204), Africa (205), or Southeast Asia (206) and systematically reviewed contributory factors in a variety of settings. Two reviews encompassed a specific pharmacological class or dosage from, including direct oral anticoagulants (207) and transdermal patches (208). One review included intern doctors only (209), while another one examined a single prespecified contributory factor (shift works) in inpatient nurses (210). Schroers et al (2020) was the only review that did not specify a population or a setting of interest (211).

Table 3. 2 Characteristics of included reviews (n=27)

Author, Year	Study design	Context	Aim	Total number of primary studies	Inclusion criteria	Exclusion criteria
Al Rowily A, 2022 (207)	Systematic review and meta-analysis	Direct oral anticoagulants (DOACs) in adult patients	To estimate the prevalence, contributory factors, and severity of ME associated with DOACs	32	Studies which reported or investigated the rate of prescribing, administration, or dispensing errors associated with DOACs in adult patients (≥ 18 years)	Studies of ADE that are not classified as errors, as were review articles, letters, opinion papers, and editorials
Aldila F, 2021 (191)	Systematic review	Community-dwelling older adults	To identify the types of medicine self-administration errors (MSEs) and their contributing factors among community-dwelling older adults	11	Older adults (≥ 50 years), self-administering of prescription or non-prescription medicines. Outcomes which met the inclusion criteria were any types of administration errors, including but not limited to, wrong medicine, wrong dose, wrong frequency, and wrong administration route	Formal caregivers or healthcare professionals administered or assisted in the administration of medicines; the studies took place in institutional care settings; and studies were not primary literature, such as non-peer reviewed publications, letters to editors, commentary, or conference presentations
Alshehri G, 2017 (200)	Systematic review	Mental health hospitals (inpatient and outpatient services)	To provide an up-to-date and critical assessment of the frequency and nature of ME and ADE in mental health hospitals	20	Studies that reported the rate of ME/ADE in one or more stage(s) of the treatment process for patients in mental health hospitals (inpatient and outpatient services), as were studies that examined the rate of unintentional medication discrepancies at the point of transition of care between mental health hospitals and other settings. Studies that examined the impact of interventions on ME or ADE	Studies that utilized incident reports as the primary source of collecting data (as they greatly underestimate the error rate) and studies that used an estimated denominator to calculate the rate of ME or ADE (as the provided rate may not be reflective of the actual rate). Studies that reported ME or ADE rates for a single drug, single drug class or disease, as were studies that only examined specific prescribing,

					rates were only included if a baseline error rate could be determined. Conference abstracts were included if they provided data sufficient to allow the rate of ME or ADE to be calculated	administration, transcription, or dispensing error subtypes. Studies that reported the rate of potentially inappropriate prescribing in mental health hospitals, as they were not considered to be ME. Review articles and studies that failed to differentiate between intentional and unintentional discrepancies using a robust method
Alsulami Z, 2013 (202)	Systematic review	Middle East countries	To identify and review studies of the incidence and types of MEs in Middle Eastern countries, and identify the main contributing factors	45	All types of studies that reported the incidence of ME or identified the causes of MEs in the Middle East countries, either in adults or children	Reviews, letters, conference papers, opinions, reports, or editorial papers
Assiri G, 2018 (102)	Systematic review	Adults managed in community care contexts	To investigate the epidemiology of ME, error-related ADE, and risk factors for errors in adults managed in community care contexts (i.e. primary care, ambulatory, and home settings)	60	Adults (≥18 years) who were looked after in the community and living in their own or family homes without home healthcare or nursing home. The studied patients could have been self-managing, receiving care in primary care or ambulatory care settings, or any combination of the above. Studies that are population-based, cross-sectional or cohort studies, which were suitable to estimate the incidence and prevalence of ME or ADE. These study designs and case–control	Pediatric studies (<18 years) and studies on patients receiving care in hospital at home settings, in nursing homes, as hospitalized inpatients or in emergency departments. RCTs since these could not be used to reliably assess the incidence and/or prevalence and reviews. Incompletely reported studies (e.g. abstracts). Studies on illegal substance abuse, herbal products and those focusing on a single medication

					studies were considered eligible to study risk factors. Studies with prescribed and/or over-the-counter medications	
Boytim J, 2018 (201)	Systematic review	Perioperative setting	To analyze the factors contributing to perioperative ME	19	Articles of any design involving the perioperative setting, ME, and human subjects	Studies not in the perioperative area; not related to MEs; animal studies; letters, opinions, reviews, or comments; and studies classified as case reports and interventions. Articles that noted the incidence of errors but had no specific details about ME and attributing causes
Di Muzio M, 2019 (210)	Systematic review	Shift work in inpatient nurses	To analyze the correlation between the clinical risk management and the occurrence of ME and the effects of the shift work (such as excessive fatigue and sleep deprivation after a shift) on inpatient nurses	19	Intervention studies, including RCT, Controlled Clinical Trials and all observational studies; papers reporting the administration of medications by registered nurses; studies performed in hospitals/inpatient settings; studies focusing on adult and pediatric patients; and peer-reviewed research articles	Studies reporting educational interventions; studies reporting the administration of medications by other HCP and studies reporting the prescription and the dispensing of drugs; studies carried out in outpatient centers, assisted living facilities and nursing homes; grey literature, such as dissertations, conference papers, proceedings

Dionisi S, 2022 (193)	Systematic review	Home care setting	To identify the main risk factors that affect the genesis of ME and the possible solutions to reduce ME in the home care setting	17	All study designs analyzing ME in the home care setting. The studies included must focus on the causes that lead to the generation of ME. Studies dealing with transitional care from any care setting to the home setting have been included. Studies in which the reference population is nurses, either as the sole reference population or in conjunction with other HCP	Grey literature (such as dissertations, conference papers, commentary, editorials) and literature reviews. All studies whose setting is different from home care, concerning hospital readmissions. Caregiver- and/or patient-centered studies, pediatric studies. Studies related to the treatment of specific diseases. The reference population is considered an exclusion criterion
Hansen C, 2016 (209)	Qualitative systematic review	Intern doctors	To synthesize the evidence of the qualitative literature on the views and experiences of intern doctors to identify the factors impacting safe prescribing and to examine the role of the pharmacist to assist in improving prescribing practices of interns	7	Only studies with qualitative data collection methods (e.g. semi-structured interviews; in-depth interviews; and original research) if they reported on newly qualified doctors' views and opinions on prescribing, and if the data from the intern doctors could be isolated from the views of other levels of staff	NR

Keers R, 2013 (196)	Systematic review of quantitative and qualitative evidence	Inpatient	To systematically review and appraise empirical evidence relating to the causes of MAE in hospital settings	55	Studies that reported data on the causes of MAE made in inpatient hospital settings. Identified causes in relation to specific errors or near misses that staff members either made themselves or were directly involved with	Review articles, conference, abstracts if they did not provide enough relevant data. Studies that reported on results based on simulation, or concerned with only one subtype of MAE, as were studies reporting results obtained from incident or case reports as it could not be determined whether the person reporting the incident had been directly involved
Lampert A, 2014 (208)	Systematic review	Transdermal patches	To systematically review the literature on nature and etiology of potential administration errors associated with the use of transdermal patches and characterized these errors according to the affected administration subprocess	42	All types of publication that reported an actual faulty administration of a transdermal patch. Demographic data (age, sex) were considered mandatory to eliminate duplicate reports and prevent subsequent distortion of results regarding the frequency of errors	Solely characteristics of a new transdermal patch were presented; the safety profile of a drug in a transdermal patch was evaluated; ADR were reported while the transdermal patch was used correctly; intentional misuse, abuse, or suicide because prevention strategies would largely differ from those applicable for unintentional errors; or no indication for causality between the faulty administration and the outcome was given
Lermontov S, 2018 (199)	Systematic review	Hematopoietic stem cell transplantation	To identify in the literature the incidence, related factors, consequences, and prevention mechanisms of ME in the context of	11	All study designs that report ME in the bone marrow transplantation scenario	Conference, abstracts, editor letters, book chapter, editorial, review, comment, and dissertation/thesis

			hematopoietic stem cell transplantation			
Lopez-Pineda A, 2022 (197)	Systematic review	Pediatric ME by parents or caregivers at home	To review the current literature on the frequency of pediatric ME by parents or caregivers at home, their associated factors, and pediatric ME reporting systems	19	Original articles on ME, either prescribed or non-prescribed drugs, that parents or other caregivers of children make at home, influencing factors and pediatric ME reporting systems. Any type of study design if they investigated ME in pediatric population in the outpatient setting (at home)	Studies on therapeutic adherence, any type of review, non-citable paper, such as editorials or letters to the editor, or studies for which access to complete information was not available, even after contacting the authors
Mansouri A, 2014 (203)	Systematic review	Iran	To detect and evaluate the studies on source of ME, reasons for ME under-reporting, preventive measures of ME and the most common drugs related to ME in Iran	25	All types of original studies on adults and children that reported sources of ME, reasons for not reporting ME, preventive measures of ME and most common drugs involved in ME in Iran	Letters, case reports, conference papers, organizational reports, opinions, or editorial papers. Articles focused on medical errors and nursing practice errors. Articles on preventive measures which were solely focused on usability and acceptability of the measures themselves, not on the outcome of reducing ME

Marznaki Z, 2020 (204)	Systematic review	Iran emergency departments	To review the literature describing the prevalence and factors affecting ME among emergency ward nurses in Iran	8	Full-text, peer-reviewed published studies that evaluated ME among emergency ward nurses in Iran	Studies conducted among any other healthcare providers, or among nurses who worked in other wards. Reviews, letters, RCTs, case studies, conference papers, opinions, dissertations, reports, and editorial papers. No access to full text. Grey literature as they usually do not portray the whole picture of the results, and when fully published, the results may change substantially
Mekonnen A, 2018 (205)	Systematic review	African hospitals	To systematically investigate the literature on the extent of ME and ADE, and the factors contributing to ME in African hospitals	41	Peer-reviewed original published articles, irrespective of the study design, that investigated the frequency and nature of ME and/or ADE. Studies that addressed ADE were included only if injuries due to medications were reported. Studies that assessed HCP experiences or possible causes of ME. Studies should be carried out in an African hospital setting	Studies that investigated failures in optimizing drug therapy (e.g. dosage adjustment in renal failure patients), pharmaceutical issues, events caused by single drugs or drug classes or disease condition, and studies that aimed to assess knowledge and attitude to ADR reporting. Studies evaluating non-adherence to medication or self-harm. Conference abstracts, case studies, commentaries, and reviews

Mira J, 2015 (192)	Systematic review	Self-administering medications at home	To review and describe the methodological approaches and results of published studies on the frequency, causes, consequences, and avoidance of ME committed involuntarily by patients on self-administering medicines at home	69	Studies that focused on empirical, review or assessment work in relation to errors made by patients in their homes. Studies on types of errors on taking medication prescribed by a doctor or as the result of self-medication, factors that brought them about and their consequences. Studies on involuntary non-adherence that contributed data on ADE due to forgetting one's medication or failing to correctly follow the therapeutic regimen. Peer-reviewed research	Studies on the frequency and causes of voluntary non-adherence. Studies on self-medication when not related to the occurrence of patient harm according to the classification of errors by Buetow et al. Studies on patients acting as vigilant partners in safety (second control) thereby helping professionals avoid ADE or on the use of medicines for suicide attempts
Parand A, 2016 (194)	Systematic review	Domiciliary setting	To review studies of how carers cause and/or prevent MAE within the patient's home; to identify types, prevalence and causes of these MAE and any interventions to prevent them	36	Errors occurred in the home, carers were responsible for the delivery of medication and empirical data were provided. Papers describing multiple case studies and qualitative studies where there was more than one care recipient participant	Papers describing a single case study, such as a MAE legal case. Papers that did not report data for carer-caused MAE separately to other ME or from other administrators (e.g. patients themselves), unless over 80% of combined data related to carers
Salmasi S, 2015 (206)	Systematic review	Southeast Asian countries	Aimed systematically to identify and review research done on ME in Southeast Asian countries to identify common types of ME and estimate its prevalence	17	All study designs. Patients of all ages from Southeast Asian countries	Reviews, letters, case studies, conference papers, opinions, reports, or editorial papers
Salmasi S, 2017 (198)	Systematic review	Older people	To systematically review studies on the	18	Original peer-reviewed research studies if they	Studies focusing on ME caused by patients, such as self-

			incidence and categories of ME in older people in any setting		comprised ME in people aged ≥55 years. The more conservative cutoff point of 55 years was chosen to ensure no relevant study was excluded. Studies were only included if they were designed to assess ME	medication. Unpublished or grey literature. Studies that reported ME as a secondary or additional outcome and those not specifically designed to assess and analyze ME. The prescribing of Beers medication was not considered a ME
Santesteban E, 2015 (195)	Systematic review	Neonatal Intensive Care Units (NICU)	To review the literature on the frequency and types of ME in NICU and the effectiveness of preventive strategies	13	Original studies or systematic reviews that measured ME in NICU and original studies or systematic reviews that measured interventions to reduce ME in NICU	Case studies or case reports; studies about errors in parenteral nutrition preparation; editorial articles or narrative reviews of ME; and abstracts without concrete results
Schroers G, 2020 (211)	Systematic review	Not specific	To critique and synthesize the qualitative evidence on perceived causes of MAE as reported by nurses in health care settings	16	Studies that used a qualitative or mixed methods design and reported qualitative data on nurses' perceived causes of MAE in health care settings	NR
Sears K, 2012 (111)	Systematic review	Community setting	To identify the incidence, prevalence and contributing factors associated with ME for children and adults in the community setting	21	All types of studies that included adults and children living in the community (including home/residential homes) that have experienced a ME and evaluated the incidence, prevalence and contributing factors	NR
Snijders C, 2007 (188)	Systematic review	Neonatal Intensive Care Units (NICU)	To examine the characteristics of incident reporting systems in NICU in relation to type, etiology, outcome,	10	Systematic reviews, RCT, observational studies, or qualitative research concerning incident reporting. NICU data can be extracted from articles	Non systematic reviews, expert opinion, case reports, letter from the editor

			and preventability of incidents			
Thomas B, 2019 (72)	Systematic review	Hospitalized patients in Middle Eastern countries	To critically appraise, synthesize and present the evidence of ME amongst hospitalized patients in Middle Eastern countries, specifically prevalence, nature, severity, and contributory factors	50	Primary research studies of any design conducted in hospital settings in the Middle East (defined) which quantified ME (i.e. prescribing, administration or dispensing errors). Studies which reported error nature, severity or associated causative factors were also included	Studies of ADE which were not classified as errors, as were review articles, letters, opinion papers, editorials, and conference abstracts
Tully M, 2009 (189)	Systematic review	Inpatient	To identify all informative published evidence concerning the causes of and factors associated with prescribing errors in specialist and non-specialist hospitals, collate it, analyze it qualitatively and synthesize conclusions	17	Studies that reported on the causes of and/or factors associated with prescribing errors in handwritten prescriptions written by doctors for adult and/or child hospital inpatients. Studies reporting ME more broadly were only included if they describe the causes of or factors associated with prescribing errors in sufficient detail to allow extraction and analysis to be carried out. Any study design with data concerning causes and associated factors collected empirically	Studies where causality or associated factors were surmised (e.g. based on professional experience of the data collector). Conference abstracts
Wimpenny A, 2010 (190)	Systematic review	Acute care settings	To undertake a comprehensive systematic review of roles and systems for	19	Participants were nurses, pharmacists, pharmacy technicians, medical and surgical staff, and adult patients	NR

			preventing ME during routine medication administration in hospital based acute care settings		in hospital-based, acute care settings. Intervention related to administration systems and related to roles of those who administer medicines were considered. The perceptions of causes of error was the phenomena of interest. Quantitative studies of ME error rates for differing medication systems and roles of those administering medications. Qualitative and descriptive studies of perceived causes of errors	
ME: medication errors; ADE: adverse drug events; RCT: randomized controlled trials; HCP: healthcare providers; ADR: adverse drug reactions; NR: not reported; MAE: medication administration errors						

3.3.3 Search details

The number of databases reported in the systematic reviews ranged from two (201, 208) to 21 (190). The most commonly recurring databases were Medline/PubMed, CINAHL, Embase, Cochrane, and British National Index (Table 3.3). Multiple reviews reported the use of both PubMed and Medline including a review that only searched these two databases (72, 191, 198, 201, 202, 205, 206). Six out of the 27 reviews did not involve resources other than the databases such as reference lists or grey literature. Most reviews applied language as a filter, largely limiting their results to English language. Few reviews (n=7) included studies of a number of languages, mainly those spoken by the research team.

The majority of reviews, except for four (189, 196, 210, 211), did not integrate keywords specific to contributory factors in their search strategy, including a review that exclusively examined contributory factors (193). One out of the four reviews included keywords specific to the contributory factor of interest (shifts work), while the remaining utilized general keywords. The general keywords were: cause(s); causality; causalities; reason(s); aetiology; etiology; factor(s); risk factor(s); contributing factor(s); determining factor(s); predictor(s); association(s); and determinants.

3.3.4 Quality assessment

All but six (188, 189, 192, 195, 203, 208) of the reviews reported quality assessment of the included articles. The two most common quality assessment tools were Allan and Barker instrument (with or without modifications) and the Critical Appraisal Skills Programme (CASP) checklist. As reported by authors, the overall quality of primary

studies included in the systematic reviews was variable (Table 3.3); with a considerable number reporting moderate overall quality.

According to the appraisal of the included systematic reviews using the JBI tool, the overall quality varied, with common areas of bias noted across reviews (Table 3.4). Most reviews described their aim (n=19; 68%) and future research directions (n=20; 74%), while 16 (59%) and 14 (52%) reviews lacked information about eligibility criteria and data extraction respectively. Some reviews did not incorporate sufficient description of their search strategy (52%; n=14) and resources (e.g. databases, grey literature, or reference lists) used to search for studies (41%; n=11). Although most reviews reported that risk of bias assessment was conducted by two independent investigators, the key limitations were related to the process of quality assessment and the methods for combining the outcomes for primary studies. Whilst around 59% (n=16) of the systematic reviews provided some description pertaining to the implication for practice, only five provided comprehensive recommendations and linked them to the identified contributory factors.

Table 3. 3 Search details and quality assessment (as reported by review) of included reviews

Author, Year	Number of databases	Databases searched	Other sources	Search timeframe	Search limits	Specific terms for contributory factors	Tools utilized to assess methodological quality	Overall methodological quality	Tools utilized to assess quality of evidence	Overall quality of evidence
Al Rowily A, 2022 (207)	6	Medline, Embase, CINAHL, BNI, IPA, CENTRAL	Yes (google scholar, grey literature, reference lists)	Database inception to September 2020	English	None	CASP checklist	Quality of the included studies was variable	Not done	Not done
Aldila F, 2021 (191)	5	PubMed, Medline, Embase, CINAHL, Scopus	Yes (google scholar, reference lists)	January 1, 2014 to June 12, 2020	English	None	Quality Assessment Tool for Studies with Diverse Designs (QATSDD)	Varied between 12% and 71%, with a mean of 56% and a median of 62% (no further explanation)	Not done	Not done
Alsheh ri G, 2017 (200)	10	Medline, Embase, CINAHL, IPA, PsycINFO, Scopus, BNI, ASSIA, Web of Science, CENTRAL	Yes (referenc e lists)	January 1999 to October 2016	None	None	Criteria adopted from Allan and Barker (10 criteria)	7.3 out of 10	Not done	Not done
Alsula mi Z, 2013 (202)	5	Embase, Medline, PubMed, BNI, CINAHL	Yes (referenc e lists)	Inception to October 2011	None	None	Criteria adopted and modified from Allan and Barker (13 criteria)	36 studies: ≤7 out of 13 5 studies: 8 out of 13 3 studies: 9 out of 13 1 study: 10 out of 13	Not done	Not done

Assiri G, 2018 (102)	6	CINAHL, Embase, Eastern Mediterranean Regional Office of the WHO, Medline, PsycINFO, Web of Science	Yes (google scholar, grey literature, reference lists)	January 1, 2006 to December 31, 2015	None	None	-CASP checklist for cohort and case-control studies -JBI Critical Appraisal Checklist for cross-sectional studies	The quality of the cross-sectional: low for 1 study, moderate for 10 studies and high for 9 studies The quality of the cohort studies: moderate for 3 studies, and high for 37 studies	Not done	Not done
Boytim J, 2018 (201)	2	PubMed, Medline	None	2000 to 2016	English	None	Not done	Not done	AORN Research Evidence Appraisal Tool	Good-level of evidence: 16 High-level of evidence: 3
Di Muzio M, 2019 (210)	4	PubMed, Scopus, Cochrane, CINAHL	None	1992 to August 2017	English and Italian	Yes (shift, shift work, work shift, work schedule)	Not done	Not done	GRADE	Not reported
Dionisi S, 2022 (193)	3	PubMed, CINAHL, Cochrane	Yes (reference lists)	January 01, 2009 to September 30, 2021	None	None	Not done	Not done	GRADE	Very low: 8 Low: 9
Hansen C, 2016 (209)	7	PubMed, Embase, CINAHL, CENTRAL, PsycINFO, Web of Science	Yes (google scholar, reference lists)	Not reported	English	None	CASP checklist	Not reported	Not done	Not done

Keers R, 2013 (196)	7	Medline, Embase, IPA, CINAHL, PsycINFO, Health Management Information Consortium, Social Science Citation Index	Yes (reference lists)	1985 to May 2013	English	Yes (cause(s), factor(s), reason(s), aetiology, etiology, causality, causalities, predictor(s), association(s))	Due to the heterogeneity of study designs, in-depth quality analysis was impractical; instead broad quality criteria were applied relating to three main interests	No overall assessment reported. The study reported detailed description of each criterion in each study. For the full details, refer to the study	Not done	Not done
Lampert A, 2014 (208)	2	Medline, CINAHL	Yes (grey literature, reference lists)	1979 to 21 January 2014	English, German, French, Spanish, Italian, Swedish	None	Not done	Not done	Not done	Not done
Lermontov S, 2018 (199)	5	Embase, CINAHL, PubMed, CENTRAL, LILACS	None	Not reported	None	None	Not done	Not done	Melnyk and Fineout-Overholt classification	Level VI of evidence: evidence derived from a single descriptive or qualitative study

Lopez-Pineda A, 2022 (197)	4	Medline (PubMed), Scopus, Embase, Science Direct	Yes (reference lists)	January 1, 2013 to May 24, 2021	English, Spanish	None	-National Institutes of Health (NIH) Quality Assessment Tools for quantitative studies -CASP checklist for qualitative studies	Poor: 2 studies Fair: 9 studies Good: 8 studies	Not done	Not done
Mansouri A, 2014 (203)	7	Scopus, Web of Science, PubMed, CINAHL, EBSCOHOST, Iran Medex, SID	Yes (reference lists)	Not reported	None	None	Not done	Not done	Not done	Not done
Marznaki Z, 2020 (204)	5	SID, PubMed, Cochrane Library, Web of Science, Scopus	Yes (google scholar, reference lists)	Database inception to December 2019	Persia, English	None	The British Sociological Association Medical Sociology Group appraisal tool	Moderate quality: 38.0% of the studies High quality: 62.0% of the studies	Not done	Not done
Mekonnen A, 2018 (205)	5	PubMed, Medline, Embase, Web of Science, Global Health	Yes (reference lists)	Databases inception to August 31, 2017	English	None	Criteria adopted from Allan and Barker (with Alsulami modifications, 13 criteria)	29 studies: ≤7 out of 13 8 studies: 8 out of 13 2 studies: 9 out of 13 1 study: 10 out of 13 1 study: 12 out of 13	Not done	Not done

Mira J, 2015 (192)	5	Medline, Web of Knowledge, Scopus, Trip database, and Index Medicus	Yes (reference lists)	January 1990 to November 2014	English, Spanish	None	Not done	Not done	Not done	Not done
Parand A, 2016 (194)	5	Embase, Medline, PsycINFO, Cochrane, CINAHL	None	January 1, 1946 and September 23, 2013	None	None	Standard Quality Assessment Criteria for Evaluating Primary Research Papers from a Variety of Fields	They provided scores for each study without an overall quality assessment. The scores varied significantly from 46.67% to 100%	Not done	Not done
Salmasi S, 2015 (206)	5	Embase, Medline, PubMed, ProQuest CENTRAL, CINAHL	None	Not reported	Human	None	Criteria adopted from Allan and Barker (with Alsulami modifications, 13 criteria)	Poor quality: 12% of studies Average quality: 47% of studies Good quality: 41%	Not done	Not done
Salmasi S, 2017 (198)	4	PubMed, EBSCOhost, Medline, ProQuest central databases	Yes (reference lists)	Database inceptions to November 2017	None	None	Criteria adopted from Allan and Barker (with Alsulami modifications and further modifications, 13 criteria)	Poor quality (<12): 2 studies Average/moderate quality (12-23): 9 studies Good quality (>23): 7 studies	Not done	Not done
Santesteban E, 2015 (195)	5	Drug information full text, Medline, Embase, EBM	None	2000 to 2013	English, Spanish	None	None	None	Not done	Not done

		Reviews, CENTRAL,								
Schroers G, 2020 (211)	3	CINAHL, PubMed, Scopus	Yes (google scholar, reference lists)	2000 to February 2019	English	Yes (causes, factors, determinants, contributing factors, determining factors)	CASP checklist	The study reported detailed description of each criterion in each study. For the full details, refer to the original articles. No overall assessment reported	Not done	Not done
Sears K, 2012 (111)	10	Medline, CINAHL, Embase, Global Health, Ageline, Cochrane, AMED, PsycINFO, Web of Science, ProQuest Dissertations	Yes (grey literature, reference lists)	1990 to 2011	English	None	JBI critical appraisal checklist for experimental studies	A cut-off point of five was established. Reduced levels of methodological rigor were evident; however no studies were excluded based on critical appraisal. The studies met the JBI level of evidence at the level of three	Not done	Not done
Snijders C, 2007 (188)	3	Medline, Embase, Cochrane	Yes (reference lists)	January 1980 to January 2006	English, Dutch, German, French	None	Not done	Not done	Not done	Not done

Thomas B 2019 (72)	5	CINAHL, Embase, Medline, PubMed, Science Direct	Yes (reference lists)	2000 to the end of March 2018	English	None	The STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) checklist	16 studies (32%): ≤4 out of 11 21 studies (42%): 5-7 out of 11 13 studies (26%): ≥ 8 out of 11	Not done	Not done
Tully M, 2009 (189)	7	Medline, Medline In-process and other Non-Indexed Citations, Embase, CINAHL, ASSIA, PsycINFO, Social Science Citation Index, IPA	Yes (reference lists)	1985 to July 2008	English	Yes (cause(s), causality, causalities, reason(s), risk factor(s), predictor(s), association)	Not done	Not done	Not done	Not done
Wimpenny A, 2010 (190)	21	Medline, Embase, Cochrane, Scopus, Scirus.com, EBM Reviews, PsycINFO, TRIP, Health Technology Assessments, BioMed CENTRAL, Current	Yes (google scholar, reference lists)	January 1990 to December 2008	English	None	Appropriate JBI quality assessment tools were used based on methodology	35 studies critically appraised and only 19 were included (according to each specific tool)	Not done	Not done

		Contents, Web of Knowledge, Web of Science, CRD, NLM Gateway, BNI, QuEST, Qualitative Inquiry, NHS National Library for Health, AHRQ, Bandolier – Evidence Based Health Care								

CINAHL: Cumulative Index to Nursing and Allied Health Literature; BNI: British Nursing Index; IPA: International Pharmaceutical Abstracts; CENTRAL: Cochrane Central Register of Controlled Trials; CASP: Critical appraisal skills programme; ASSIA: Applied Social Sciences Index & Abstracts; GRADE: Grading of Recommendations, Assessment, Development and Evaluations; SID: Scientific Information Database; TRIP: Turning Research into Practice; CRD: Centre of Reviews and Dissemination; QuEST: Qualitative Evidence Synthesis Texts

Table 3. 4 Quality assessment of included reviews

Author, Year	Is the review question clearly and explicitly stated?	Were the inclusion criteria appropriate for the review question?	Was the search strategy appropriate?	Were the sources and resources used to search for studies adequate?	Were the criteria for appraising studies appropriate?	Was critical appraisal conducted by two or more reviewers independently?	Were there methods to minimize errors in data extraction?	Were the methods used to combine studies appropriate?	Was the likelihood of publication bias assessed?	Were recommendations for policy and/or practice supported by the reported data?	Were the specific directives for new research appropriate?
Al Rowily A, 2022 (207)	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Aldila F, 2021 (191)	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Not appropriate	Yes	Yes
Alshehri G, 2017 (200)	No	No	Yes	No	Yes	Unclear	Unclear	No	Not appropriate	No	Yes
Alsulami Z, 2013 (202)	No	Yes	Yes	No	No	Unclear	No	No	Not appropriate	No	Unclear
Assiri G, 2018 (102)	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Not appropriate	Yes	No
Boytim J, 2018 (201)	Yes	Yes	No	No	No	Unclear	No	No	Not appropriate	Yes	Yes
Di Muzio M, 2019 (210)	Yes	No	No	No	No	Unclear	No	No	Not appropriate	Yes	Yes
Dionisi S, 2022 (193)	Yes	No	No	No	No	Unclear	Yes	No	Not appropriate	Yes	Yes
Hansen C, 2016 (209)	Yes	Yes	No	Yes	Yes	Unclear	Unclear	Yes	Not appropriate	No	Yes
Keers R, 2013 (196)	Yes	Yes	No	Yes	No	No	Yes	Yes	Not appropriate	No	Yes
Lampert A, 2014 (208)	Yes	Yes	Yes	No	No	Unclear	Yes	Yes	Not appropriate	No	No

Lermontov S, 2018 (199)	Yes	No	No	No	No	Unclear	Unclear	No	Not appropriate	No	No
Lopez-Pineda A, 2022 (197)	No	No	No	Yes	Yes	Yes	Yes	No	Not appropriate	No	No
Mansouri A, 2014 (203)	Yes	Yes	Yes	Yes	No	No	No	Yes	Not appropriate	No	Yes
Marznaki Z, 2020 (204)	No	No	Yes	Yes	Yes	Yes	Yes	No	Not appropriate	Yes	No
Mekonnen A, 2018 (205)	Yes	Yes	Yes	Yes	Yes	No	No	No	Not appropriate	Yes	Yes
Mira J, 2015 (192)	No	Yes	Unclear	Yes	No	No	Unclear	No	Not appropriate	Yes	Yes
Parand A, 2016 (194)	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Not appropriate	Yes	Yes
Salmasi S, 2015 (206)	Yes	No	No	No	Yes	Unclear	Unclear	No	Not appropriate	No	No
Salmasi S, 2017 (198)	Yes	Yes	Yes	No	No	Yes	Yes	No	Not appropriate	Yes	Yes
Santesteban E, 2015 (195)	No	No	Unclear	No	No	No	No	No	Not appropriate	No	No
Schroers G, 2020 (211)	Yes	No	No	Yes	Yes	Unclear	Yes	Yes	Not appropriate	Yes	Yes
Sears K, 2012 (111)	Yes	Yes	No	Yes	Yes	Yes	Unclear	Yes	Not appropriate	Yes	Yes
Snijders C, 2007 (188)	No	No	Yes	Yes	No	No	Yes	No	Not appropriate	No	Yes
Thomas B, 2019 (72)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not appropriate	No	Yes
Tully M, 2009 (189)	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Not appropriate	Yes	Yes
Wimpenny A, 2010 (190)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not appropriate	Yes	Yes

3.3.5 Medication errors: terminology, definitions, and classifications

Most reviews investigated medication errors without associating them with the stages of the medication use process (n=17); of which one review used the terms ‘medication errors’ and ‘adverse drug events’ (ADE) interchangeably (210). The remainder of the reviews focused on a single stage in the medication use process, specifically administration errors (n=4), administration errors by patient or caregiver (n=4), and prescribing errors (n=2).

Of the studies reporting on medication errors, four adopted the NCCMERP definition (198, 200, 204, 206) and four worked with the definitions provided in the primary studies (102, 111, 188, 207). Two of the reviews on administration errors by patient or caregiver provided definitions in their methods section, of which one was suggested by the authors themselves (191, 199). Two different definitions were given for administration errors (194, 196). Both were adopted from previous studies and entailed the deviation between prescribed and administered medication. As for prescribing errors, one of the reviews reported that they adopted the working definitions in the original studies (189).

Medication errors were classified in eleven of the included reviews (Table 3.5), of which 10 reported errors according to the medication use process stages (e.g. prescribing errors). The remainder investigated self-administration errors and reported according to the incident type (e.g. wrong dose) (191). Among the 10 reviews, six further classified medication errors according to the incident type (197, 200, 202, 205-207).

Table 3. 5 Data pertaining to medication errors

Author, Year	Terminology	Definition	Methodology for classifying ME	Classification of ME
Al Rowily A, 2022 (207)	Medication errors	Worked with the definitions provided by original studies	Medication use process Incident type (type of prescribing errors)	Prescribing, administration, dispensing errors
Aldila F, 2021 (191)	Medicine self-administration errors (MSE)	A deviation by the patients or their caregivers from the prescriber's medication orders or the manufacturer's administration instructions during the medicine administration process (adopted)	Types of MSE were classified in accordance with how they were reported in the original studies Incident type (type of prescribing errors)	Dosing error, missed dose, wrong medicine, duplicity of medicines, incorrect preparation methods, incorrect administration methods, wrong administration route, wrong administration time, wrong frequency, incorrect spacing (time period between doses), and use of expired medicines
Alshehri G, 2017 (200)	Medication errors	NCCMERP definition (adopted)	Medication use process Incident type (type of prescribing errors)	Overall ME, prescribing, administration, transcribing, dispensing errors
Alsulami Z, 2013 (202)	Medication errors	Not reported	Medication use process Incident type (type of prescribing errors)	Prescribing, transcribing, administration errors
Assiri G, 2018 (102)	Medication errors	Worked with the definitions provided by original studies	Medication use process	Prescribing, monitoring errors
Boytim J, 2018 (201)	Medication errors	Not reported	Not done	Not done
Di Muzio M, 2019 (210)	Medication errors and adverse events interchangeably	Not reported	Not done	Not done

Dionisi S, 2022 (193)	Medication errors	Not reported	Not done	Not done
Hansen C, 2016 (209)	Prescribing error	Not reported	Not done	Not done
Keers R, 2013 (196)	Administration errors	A deviation from the prescriber's medication order as written on the patient's chart, manufacturers', instructions, or relevant institutional policies (adopted)	Not done	Not done
Lampert A, 2014 (208)	Medication errors	Not reported	Not done	Not done
Lermontov S, 2018 (199)	Pediatric medication error at home	Any preventable and unintentional deviation from the appropriate use of prescribed or non-prescribed pediatric medication, committed by parents or caregivers in the outpatient setting	Incident type (type of errors)	Dosing errors, time administration errors, frequency errors, medication preparation method, self-decided treatment discontinuation, wrong medicine, expired medication,
Lopez-Pineda A, 2022 (197)	Medication errors	Not reported	Not done	Not done
Mansouri A, 2014 (203)	Medication errors	Not reported	Not done	Not done
Marznaki Z, 2020 (204)	Medication errors	NCCMERP definition (adopted)	Medication use process Incident type (for all stages)	Ordering, transcribing, dispensing, administration, and during medication history taking
Mekonnen A, 2018 (205)	Medicine self-administration errors (MSE)	Not reported	Not done	Not done
Mira J, 2015 (192)	Medicine self-administration errors (MSE)	Not reported	Not done	Not done
Parand A, 2016 (194)	Administration errors	Any deviation between the medication prescribed and that administered (adopted)	Not done	Not done
Salmasi S, 2015 (206)	Medication errors	NCCMERP definition (adopted)	Medication use process Incident type (type	Medication use process: prescribing, administration, dispensing, preparation, transcribing Incident type: wrong dose, omission error,

			of prescribing errors)	incorrect time, wrong drug, incorrect administration technique, wrong dose form
Salmasi S, 2017 (198)	Medication errors	NCCMERP definition (adopted)	Medication use process	Prescribing, administration, dispensing, transcribing
Santesteban E, 2015 (195)	Medication errors	Not reported	Not done	Not done
Schroers G, 2020 (211)	Administration errors	Not reported	Not done	Not done
Sears K, 2012 (111)	Medication errors	Worked with the definitions provided by original studies	Worked with the classification provided by original studies Medication use process was identified	Prescribing, administration, dispensing errors
Snijders C, 2007 (188)	Medication errors (study concerned medical errors with focus on ME)	Worked with the definitions provided by original studies	Not done	Not done
Thomas B, 2019 (72)	Medication errors	Not reported	Medication use process	Prescribing, administration dispensing errors
Tully M, 2009 (189)	Prescribing errors	Worked with the definitions provided by original studies	Not done	Not done
Wimpenny A, 2010 (190)	Administration errors	Not reported	Not done	Not done

3.3.6 Contributory factors to medication errors: terminologies, definitions, and classifications

The terms used to describe contributory factor are presented in Table 3.6. The most common term was “contributory factor”, with some reviews using “factor” alone or proceeded with another term such as “risk”, “associated”, “related”, “influencing”, “causal”, “causative”, or “etiological”. The other commonly reported term was “cause” and its derivatives including “root cause”, “causation”, and “causality”. Other less commonly used terms were “reason”, etiology”, “predictor”, and “source”.

Two included reviews defined risk/contributory factors (189, 197), while another adopted the definition of hazard/contributory factors suggested by the WHO (111). Tully et al (2009) differentiated between the terms “causes” and “contributory factors”, in which the latter was suggested to refer to those assessed by the researcher while the former referred to those identified by practitioners (189).

All but three (198, 200, 206) of the included reviews specifically aimed to explore contributory factors (Table 3.6). Ten systematic reviews had a prespecified methodology to identify and classify contributory factors, namely the use of theories/frameworks/models and thematic analysis. Four adopted Reason’s Accident Causation Model (72, 189, 196, 207), of which three classified contributory factors into categories of: active failures, error-producing conditions, and latent conditions. In their review of administration errors, Keers et al (2013) adopted a version of the theory that has been modified for administration errors (196). Amongst the included reviews that used Reason’s model, active failures and decision-making mistakes, which includes

failure to consider risk factors (e.g. chronic kidney disease and pediatrics) were the most prevalent categories of contributory factors (Table 3.7).

The Framework for Analyzing Risk and Safety in Clinical Medicine was applied by one review (42). This framework categorizes factors into six groups: individual, work environment, organization and management, team, tasks, and medications (68, 203). Another review utilized the Conceptual Framework for the International Classification for Patient Safety proposed by the WHO (111). This framework comprises 10 high-level classes and the contributing factors segment consists of a maximum of five levels (Table 3.7) (212).

Qualitative synthesis was used in four of the included reviews to categorize contributory factors. Of these, thematic analysis was applied in two, detailing generation of codes and themes (209, 211). Other methods reported were meta-regression (190) and inductive analysis (194) but with little detail provided. The review of Assiri et al (2018) had three prespecified categories (102), while four reviews classified factors according to emerging themes (192, 193, 201, 205).

Among reviews that did not follow Reason's theory, the most recurring themes were practitioner-related (n=8) and work environment-related (n=7), followed by patient-related (n=5) and medication-related factors (n=4) [Table 3.7].

Table 3.7 gives the most commonly reported contributory factors. Decision-making mistakes (classified as active failure by Reason's theory) such as failure to consider risk factors (e.g. chronic kidney disease and pediatrics) were reported in multiple systematic

reviews. Other recurring factors were related to the organization or environment, including lack of knowledge, insufficient training, work overload, inadequate staffing levels, illegible prescriptions, distraction and interruptions, and poor communication. Polypharmacy, extreme age (elderly or pediatrics), and limited health literacy of patient were also common across reviews.

Table 3. 6 Data pertaining to contributory factors to medication errors

Author, Year	How many studies reported on contributory factors	Terminology used to describe contributory factors	Definition of contributory factors
Al Rowily A, 2022 (207)	27 out of 32 (84.4%)	Contributory factors, causation	Not reported
Aldila F, 2021 (191)	7 out of 11 (63.6%)	Contributory factors	Not reported
Alshehri G, 2017 (200)	5 out of 20 (25%)	Factors that increase the risk/rate of error	Not reported
Alsulami Z, 2013 (202)	12 out of 45 (26.7%)	Contributory factors, causes	Not reported
Assiri G, 2018 (102)	36 out of 60 (60%)	Risk factors	Not reported
Boytim J, 2018 (201)	All studies (part of the inclusion criteria)	Contributory factors	Not reported
Di Muzio M, 2019 (210)	All studies (part of the inclusion criteria)	Factors, reasons	Not reported
Dionisi S, 2022 (193)	All studies (part of the inclusion criteria)	Risk factors, causes	Not reported
Hansen C, 2016 (209)	All studies (part of the inclusion criteria)	Factors influencing/ affecting prescribing behavior	Not reported
Keers R, 2013 (196)	All studies (part of the inclusion criteria)	Causes	Reasons reported to the researcher by the person directly involved with a specific administration error or near miss as being wholly or partly responsible for said error (developed by authors)
Lampert A, 2014 (208)	8 out of 42 (19%)	Contributing factors, causes, root cause, etiology	Not reported
Lermontov S, 2018 (199)	8 out of 11 (72.7%)	Related factors	Not reported
Lopez-Pineda A, 2022 (197)	14 out of 19 (73.7%)	Associated/influencing/risk factors	Any factor that increased the chance of parents or caregivers made a ME at home (developed by authors)
Mansouri A, 2014 (203)	12 out of 25 (48%)	Contributory factors, sources	Not reported

Marznaki Z, 2020 (204)	All studies	Contributory factors, factors affecting ME	Not reported
Mekonnen A, 2018 (205)	15 out of 41 (36.6%)	Contributory factors, causality	Not reported
Mira J, 2015 (192)	36 out of 69 (52.2%)	Causal factors, causes	Not reported
Parand A, 2016 (194)	25 out of 36 (69.4%)	Contributory factors, causes	Not reported
Salmasi S, 2015 (206)	15 out of 17 (88.2%)	Contributory factors, root causes	Not reported
Salmasi S, 2017 (198)	13 out of 18 (72.2%)	Contributory factors, risk factors, reasons	Not reported
Santesteban E, 2015 (195)	5 out of 13 (38.5%)	Causes	Not reported
Schroers G, 2020 (211)	All studies (part of the inclusion criteria)	Contributory factors, causes	Not reported
Sears K, 2012 (111)	10 out of 21 (47.6%)	Contributory factors, causal factors, causative factors, predictors	The circumstances, actions or influences which are thought to have played a part in the origin or development of an incident or to increase the risk of an incident (adopted from WHO)
Snijders C, 2007 (188)	All studies	Contributory factors, etiology, factors, etiological factors	Not reported
Thomas B, 2019 (72)	24 out of 50 (48%)	Contributory factors, causative factors, causes	Not reported
Tully M, 2009 (189)	All studies (part of the inclusion criteria)	Factors associated, causes	-Factors associated: variables that were linked with the prevalence of specific prescribing errors by the researchers -Causes: reasons reported to the researchers by the prescriber, in structured or unstructured interviews (developed by authors)
Wimpenny A, 2010 (190)	11 out of 19 (57.9%)	Causes, reasons	Not reported

Table 3. 7 Contributing factors to medication errors

Author, Year	Methodology to identify and classify contributory factors	Error classes		Examples	Most reported
Al Rowily A, 2022 (207)	Reason's accident causation model	Active failures	Slips	Duplicate therapy, transcription errors, dispensing errors	Active failures: mistakes
			Lapse	Acronym errors, wrong label	
			Mistakes	Wrong dose (non-consideration of renal function), wrong indication	
			Violation	Doctor not writing the order in time	
		Error provoking condition		Lack of knowledge and experience, inadequate monitoring, system errors, failure staff to follow policy, inadequate laboratory results, poor communication, distraction, work overload	
		Latent conditions		Lack of medication reconciliation service, lack of training	
Aldila F, 2021 (191)	Not reported	Not reported		Complex regimens, cognitive decline, lack of knowledge, negative attitudes and beliefs towards medicines, decline in physical ability, lack of social support, multiple chronic conditions, poor collaboration between patients/HCP and among HCP, pharmaceutical products and packaging design, confusion about compliance aids, limited health literacy, absence of error detection mechanisms, absence of patient education	Complex regimens
Alshehri G, 2017 (200)	Not reported	Not reported		Senior physicians, use of an electronic prescription pro forma, number of medications/doses, interruptions, patient load, nonoral route of administration, presence of organic brain disease (e.g. dementia), swallowing difficulties	Not reported
Alsulami Z, 2013 (202)	Not reported	Not reported		Lack of knowledge, poor compliance with guidelines, lack of reporting of ME, heavy workload and new staff, miscommunications between HCP	Lack of knowledge
Assiri G, 2018 (102)	Predefined categories	Patient-related		Polypharmacy, increased age, number of diseases, female, low level of education, hospital admission, middle family income	Not reported
		Healthcare professionals-related		Multiple physicians involved in care, family medicine specialty, age ≥51 years, male, frequent changes in prescription, not considering prescriptions of other physicians, inconsistency in the information and outpatient clinic visits	

		Medication-related	Multiple drug storage locations, expired medication, discontinued drugs repeats retained, hoarding of drugs, therapeutic duplication, no administration routine, poor adherence, confusion between generic and trade names, multidose drug dispensing users, receiving anticoagulant therapy, use of over-the-counter drugs	
Boytim J, 2018 (201)	Factors grouped according to emerging themes (not predefined)	Types of errors	Wrong dose, omission, wrong route, wrong dosage form	Performance deficits, distraction, haste, inattention, poor communication, knowledge deficits, labeling mistakes, and syringe swaps
		Causes of errors	Labeling mistakes and syringe swaps, performance deficit, distraction, poor communication, haste, inattention, knowledge deficit	
		Human factors	Haste, stress, pressure, distraction, decreased vigilance, fatigue, inaccurate medication reconciliation, patient lack of understanding, and knowledge deficit related to patient allergies	
		Medication types	Analgesics, antibiotics, vasopressors	
		Environmental factors	Transfers, fragmentation, change providers, work overload, federally owned facilities, facilities with 100 to 499 beds (compared to <100 or > 500), anesthesia induction period, maintenance period, longer procedures, procedures performed during the day	
		Patient characteristics	Low physical status, male, acuity	
Di Muzio M, 2019 (210)	Not reported	Study focused on shift works only	Occasional night shifts, reduced staffing, long shifts, work overload, sleep quality and quantity, stress, fatigue, workflow interruptions	Not reported
Dionisi S, 2022 (193)	Factors grouped according to emerging themes (not predefined)	Transition of care	Lack of complete documentation particularly medications, poor communication, technology errors, patient-related factors (elderly, polypharmacy, chronic diseases)	Not reported
		Medication reconciliation	Lack of a standardized process, lack of single documentation that reports the entire patient history, poor communication, poor flow of information	
		Multidisciplinary team	Poor interprofessional communication and with the patient, low health literacy, cognitive and functional impairment, inadequate integration of the pharmacist into the care team	
Hansen C, 2016 (209)	Thematic synthesis (predefined)	Environmental factors	Time constraints, poor communication, defenses (I know someone else will check it), hierarchical structures, rotation	Not reported
		Patient characteristics	Complexity, poor communication, patients' influence	

		Individual factors	Wellbeing (workload), lack of knowledge, attitude and awareness, responsibility, experience	
Keers R, 2013 (196)	Reason's accident causation model	Unsafe acts	Slips, lapses, knowledge-based mistakes, deliberate violations	Slips, lapses, knowledge-based mistakes, communication, work overload, medicine supply and storage
		Error-provoking conditions (local workplace factors)	Inadequate written communication, problems with medicines supply and storage, work overload, problems with ward-based equipment (access, functionality), patient factors (acuity), staff health status (fatigue, stress), interruptions	
		Organizational (high-level) decisions	Poor feedback on errors and lack of nurse input in the process, lack of hospital policy or misguided policy (low nurse staffing), logistical strategy decisions revolve around clashes of other ward activities with medication administration, look or sound alike medication may have roots beyond hospitals with the pharmaceutical industry	
		Latent conditions	Local working culture and high-level managerial decisions	
Lampert A, 2014 (208)	Not reported	Not reported	Lack of knowledge and awareness of the importance of a correct administration practice, patch designs	Not reported
Lermontov S, 2018 (199)	Not reported	Not reported	Over-the-counter medications, polypharmacy, lack of double checking, look alike and sound alike medications, stress, dose calculation error, poor communication, illegible prescriptions	Not reported
Lopez-Pineda A, 2022 (197)	Not reported	Not reported	Poor comprehension, complex regimens, low health literacy, primary language of the parent was different from the language of written discharge instructions, male sex, younger age, polypharmacy, use of dropper (versus cup and syringe), use of a teaspoon-only label, receiving text only instructions (versus text and pictogram), decreasing child age, limited understanding about medications, lack of reassessment by HCP	Not reported
Mansouri A, 2014 (203)	Framework of factors influencing clinical practice and contributing to adverse events (with modification, added an extra category entitled medication)	Individual factors	Inadequate knowledge, miscalculations of doses, physical and mental health	Individual factors: inadequate knowledge
		Work environment	Heavy workload, working overtime, nurses' burnout, little time spent with patient	
		Organization and management	Shortage of workforce (understaffing)	
		Team	Illegibility of orders or patient charts	
		Tasks	Lack of guidelines	
		Medications	Name similarity	

Marznaki Z, 2020 (204)	Not reported	No attempt at classifying by authors	Reduced staffing, inappropriate nurse-patient ratios, inadequate knowledge, demographic factors (nurses' age, gender, and work experience), busy nature of emergency wards, managerial lapses	Reduced staffing and inappropriate nurse-patient ratio
Mekonnen A, 2018 (205)	Factors grouped according to emerging themes (not predefined)	Individual factors	Fatigue, confusion, memory lapses, rushing, inadequate monitoring/reporting, inadequate knowledge/training, rule violation, inappropriate administration technique, low morale	Individual factors: fatigue and inadequate knowledge/ training Environmental factors: workplace distraction and work overload
		Working environment	Work overload, distraction, busyness, lack of resources (e.g. equipment), time of the day	
		Team	Communication deficits, no senior support	
		Task	Lack of documentation, labelling deficits, transcription error, illegible writing, multi-tasking, unfamiliar patient, look-alike drug names/labelling, syringe swap, misidentification of drugs/ampoules, careless checking/not checking	
Mira J, 2015 (192)	Factors grouped according to emerging themes (not predefined)	Intrinsic factors	Patients' profile (age, cognitive state, polypharmacy), level of health literacy	Not reported
		Extrinsic factors	Quality of the information provided, communication with caregivers, complexity of use dispensing devices	
Parand A, 2016 (194)	Contributory factors inductively identified and grouped into a new framework	Individual care recipient factors	Younger child age	Not reported
		Individual carers factors	Age of carer, educational level of carer, carer's time and other responsibilities, language of carer, health of carer, carer marital status	
		Medication factors	Polypharmacy, type of medication, route of administration, medication supply	
		Environmental factors	Storage, equipment	
		Prescription communication factors	Communication with healthcare professionals & carers' understanding of instructions or medication/illness, dosage change	
		Psychological factors	Panic/cognitive failure, fear of spillage, carer-to-carer communication	
Salmasi S, 2015 (206)	Not reported	Not reported	Factors extrapolated from original studies: staff shortage, work overload, distraction, incorrect interpretation of prescription/medication chart, lack of knowledge, lack of experience Factors provided based on the authors of the reviews assessment: poorly designed work environments and systems, patients factors (forgetfulness, lack of cooperation or confusion)	Not reported

Salmasi S, 2017 (198)	Not reported	Not reported	Polypharmacy, inappropriate administration scheduling, understaffing, similar packaging, stress and time constraints, lack of staff training, medications associated with complex tasks (crushing), interruptions during ward rounds	Not reported
Santesteban E, 2015 (195)	Not reported	Not reported	Human factors, use of unlicensed medicines,	Human factors
Schroers G, 2020 (211)	Thematic synthesis (methods predefined)	Knowledge-based factors	Lack of knowledge about medications, protocols, technology, calculations, lack of skills required for administration, misinterpretation of preparation protocols	Contextual factors (most common): heavy workloads and interruptions Knowledge-based factor: medication knowledge Personal factors: fatigue and complacency
		Personal factors	Complacency, lack of confidence, fear of looking incompetent, overconfidence, negligence, forgetfulness, lack of attentiveness, not following protocol, practice beyond scope of practice, fatigue, tendency to make assumptions, stress, lapses, nervousness, lack of concentration, lack of care, unpreparedness, drowsiness, talking, multitasking, personal or family health issues, deliberate deviations from guidelines	
		Contextual	Interruptions, poor communication, challenging professional relationships, understaffing, heavy workloads, lack of supervision/support, inexperience, lack of training, improper physical working conditions, work-related pressure, lack of time, unsafe practice norms	
Sears K, 2012 (111)	Analyzed using the Conceptual Framework for the International Classification for Patient Safety proposed by the WHO	Staff factors	Cognitive factors: lack of knowledge, confusion about medications Performance factors: dosing errors, misreading prescriptions, calculation errors Behavior factors: fatigue, carelessness, lack of concentration Communication factors: poor communication, lack of communication between doctor and patient or between staff, patient and carers Emotional factors: low satisfaction	Not reported
		Patient factors	Cognitive factors: confusion, lack of awareness of medications Performance factors: dosing errors	
		Work/environment factors	Physical environment/infrastructure: hot, airless, poorly lit, short of space, busy environment, pressured, noisy and fraught, interruptions	
		Organizational/service factors	Resources/workload: busy, distraction	

		External factors		Products, technology, and infrastructure: similar looking medications/containers/ packaging, similar drug names	
Snijders C, 2007 (188)	Not reported	Not reported		Failure to follow procedures, inattention, poor documentation or communication, lack of training, negligence, poor regulation, incorrect orders, faulty preparation, increased level of care, verbal orders differed from written order, lack of double check, dose miscalculations -Some studies reported the stage of the medication use process or the incident type as the contributory factor	Not reported
Thomas B, 2019 (72)	Reason's accident causation model	Active failure	Slips	Look-alike sound-alike medications, selecting wrong medication, wrong patient, memory lapses	Active failures: slips, lapses, and mistakes Error-provoking conditions: lack of knowledge, insufficient staffing levels Latent conditions: heavy workload
			Lapses	Dispensing errors, failure to give medication, lack of documentation, faulty dose checking	
			Mistakes	Wrong dose, wrong packaging, incomplete medication orders, incorrect transcription	
			Violation	Use abbreviations, poor adherence to protocol, using acronyms	
		Error- provoking conditions		Fatigue, illegible handwriting, work overload, patient condition (illiteracy, elderly)	
		Latent conditions		Lack of training, lack of staffing, poor communication, supervisory issues, lack of policy and procedures, performance deficit	
Tully M, 2009 (189)	Reason's accident causation model	Active failure	Slips	Skill-based	Active failure: mistake
			Lapses	Memory-related	
			Mistakes	Knowledge-based, rule-based	
			Violation	Inadequate monitoring, not following policy	
		Error- provoking conditions		Lack of training or experience, fatigue, stress, high workload for the prescriber and inadequate communication between HCP	
		Latent conditions		Reluctance to question senior colleagues, inadequate provision of training	
Wimpenny A, 2010 (190)	Results were combined in a meta-aggregative view	Quantitative data from nurses' perception		Nurse fails to check patients name band with the medication administration record, tired and exhausted, order difficult to read or illegible, distracted by other patients, co-workers or events, dose miscalculation	Not reported

		Qualitative data from nurses' perception	External factors: use of policies, protocols, and guidance; context and organization of care; and roles of people within the system Internal factors: interpersonal skills and relationships; individual knowledge and skills; and personal responsibility	
		Qualitative data from patients' perception	Patients not included in the medication administration process; nurses may not listen to their concerns; and patients unaware of the medication administration process and the drugs being administered	
HCP: healthcare providers; ME: medication errors				

3.3.7 Interventions proposed to mitigate factors contributing to medication errors

None of the reviews aimed to evaluate interventions designed to mitigate contributory factors. Nevertheless, 21 included reviews discussed interventions without specifying the characteristics, method of development, and outcomes of these interventions. Multiple reviews emphasized the need for multifactorial interventions to holistically address contributory factors, (102, 111, 189-191, 193, 194, 199, 201, 204, 207). Only one review suggested the use of theory to develop these interventions (207).

Pharmacist-delivered (102, 191, 193, 201, 205-207), educational (102, 111, 194, 199, 202, 204, 205, 207, 208, 211) and technology-enabled interventions (102, 192-194, 199, 201, 204, 205, 207) were most frequently suggested in the included reviews. Only two included reviews incorporated organization-level interventions (e.g. increase staffing) (204, 211).

Among studies that recommended pharmacist-delivered interventions, four suggested full integration of the pharmacist in the healthcare team (102, 201, 205, 206) while three recommended initiating a pharmacist-led service (e.g. anticoagulation stewardship program) (191, 193, 207). Most reviews that suggested technology-enabled interventions highlighted the need for decision support systems to reduce prescribing errors (204, 205). Three studies proposed the development of innovative technological tools (e.g. mobile application) that could be accessed by patients and tailored to their needs (102, 192, 194).

Proposed educational interventions varied significantly among the included studies based on the context. For instance, studies that focused on administration errors, recommended

distributing educational material alongside the educational sessions for the nurses to refer to it when needed (192, 211). Nevertheless, a common suggested topic was the communication and interprofessional collaboration between different healthcare providers (189, 193, 194, 207, 211). Few reviews reported that educational sessions should be conducted periodically (199, 204).

3.4 Discussion

3.4.1 Statement of key findings

This umbrella review shows that decision-making mistakes, which includes non-consideration of risk factors (e.g. chronic kidney disease and pediatrics) were the most common contributory factor, followed by factors related to the organization and environment such as the lack of knowledge/training, understaffing, and distractions. Most reviews did not prespecify a methodology in relation to classification of contributory factors. Amongst the reviews that followed a structured method to classify contributory factors, the use of theory and Reason's model was most commonly used. The included reviews were of variable quality due to issues primarily related to search strategy, quality assessment, and data extraction processes. A range of terminologies and definitions were used to refer to contributory factors. To target the contributory factors and subsequently reduce the errors, several interventions were suggested in the included reviews. These included pharmacist-provided, education, and technology-based interventions. The discussion of interventions lacked details on the development, evaluation, and implementation.

3.4.2 Interpretation of findings

Decision-making mistakes (also known as error of judgment), which includes failure to consider risk factors (e.g. chronic kidney disease and pediatrics) was the predominant contributory factor to medication errors across diverse healthcare settings. Decision-making mistakes and other types of human errors are foreseeable in the context of the complex and often challenging clinical practices (213). Additionally, healthcare is dynamic in nature with a great deal of uncertainty and potential subjectivity surrounding clinical decisions (213, 214). Therefore, although it is imperative to attempt at mitigating these mistakes, it is unrealistic to expect an error-free system. However, innovative theory-based interventions that promotes multidisciplinary team working, blame-free culture, use of technology, and expertise of pharmacists can minimize errors.

Another common contributory factor identified in this umbrella review related to organizational and environmental factors. These factors have been poorly reported in previous literature as less attention has been given to error-prone systems (215).

Although the use of theoretical framework has been strongly recommended to undertake exploratory and interventional research to identify and target different behaviors (64, 216), most of the reviews did not report a prespecified method to synthesize contributory factors, with only six using a theory-based approach. One recurring model to classify contributory factors was Reason's model. This model shifts the focus of human errors investigation from person-centered to system approach considering errors occurring at both the sharp (active failures) and blunt (latent conditions) ends of the system (38, 217). The model also moves away from blame culture while still being easy-to-use; thus it has

been extensively utilized in the safety field (38, 218). Nonetheless, Reason's model has limitations that should be considered by researchers who use it as well as practitioners who interpret findings from studies that have used it. The model is considered a complex linear model which assumes that accidents are the result of series of events that interact sequentially in a linear fashion (219). This approach may overlook the complexity of the system and interrelations between its components, particularly when the contributory factors are far from the incident in terms of time or location (65, 219). Furthermore, some researchers argue that Reason's theory may not account sufficiently for the interactions between defense layers and the errors produced by the defense mechanisms (217).

Seventeen different terms and five definitions were used by the reviews to describe contributory factors. Variations in the definition of medication error (and subclasses) were also noted amongst the reviews. This reinforces findings from previous arguments suggesting multiplicity in the use of patient safety practice related terminologies (17, 21, 111, 207). It is likely that an array of definitions for both medication errors and contributing factors used by other literature may not be captured by reviews included in this study.

It is worth noting that the primary studies that focused on interventions to mitigate errors were prospective/retrospective cohort studies or cross-sectional studies (220-227). A definitive evaluation utilizing randomized controlled trials was missing. Additionally, the majority of studies had a short follow-up duration, a small sample size, and were conducted in a single center (220-227). The primary outcome measure evaluated in these studies mainly related to the number of interventions offered such as changing one of the components of a medication regimen (e.g. dose, duration) or highlighting an interaction

between prescribed drugs. Another outcome measure was the total number of errors that were assessed to be potentially preventable upon implementing the interventions (220-227).

3.4.3 Strengths and limitations

This is the first attempt to systematically report the terminology, methodology, and classes of contributory factors to medication errors via an umbrella review. A comprehensive search of several databases followed by citation checking allowed retrieval of all relevant systematic reviews.

This review was limited by the lack of assessment for the potential overlap of individual studies within the included reviews. In addition, our summary of terms and definitions on contributory factors and medication errors relied on what has been reported by the included reviews. Lastly, only publications in English language were included.

3.4.4 Implication for practice and research

Although the context of existing systematic reviews varied, several contributory factors were common across the reviews. The comprehensive synthesis of these factors could enable the development of holistic theory-informed interventions to target the identified factors. The identified contributory factors included decision-making mistakes and organizational factors. Accordingly, multifaceted theory-based interventions are required to prevent medication errors. These interventions should target contributory factors from the organizational level to specific tasks at the individual level.

Failure to account for risk factors was a common example of decision-making mistakes. Previous studies have shown that pharmacist-led and technology-enabled interventions minimize medication errors, including those occurring in high-risk cohorts (228-230). Although the role of pharmacists and technology has expanded in recent years (228-230), their expertise remain underutilized (231-234).

System failures due to top-level management decisions were also identified among the most recurring contributory factors, of which inadequate training and knowledge was predominant. This indicates that limited continuing professional development activities alone might be insufficient in terms of quantity or quality. A previous systematic review showed that pharmacist-conducted educational interventions led to a significant reduction in medication errors rates (134). Accordingly, implementation of educational sessions that are based on a structured needs assessment to address the exact gaps in knowledge are likely to impact positive changes (235).

Despite the continuous growth of healthcare costs, issues related to understaffing and poor work environment were still prominent in this review. Hence, strategic allocation of available resources and implementation of cost-effective mitigation mechanisms is recommended. Moreover, organizational and environmental factors that lead to breakdowns in communication and collaboration between healthcare providers have been repeatedly reported across the included reviews. Thus, interdisciplinary collaborations could be considered in future interventions as they represent an important facet of facilitating communication (236). This is particularly important as medication errors are a complex problem affecting diverse healthcare disciplines and contexts.

Additionally, it is pivotal that healthcare systems move to a blame-free and non-punitive culture. It is also important that subject matter and safety experts provide timely and systems-oriented solutions and feedbacks to the reported errors in a confidential manner (237). This will encourage healthcare providers to report and disclose medication errors, which will allow policy makers to accuretly estimate the extent of the problem and understand the exact contributory factors and offer support.

It is evident from the findings of this review that there are certain populations/settings for which contributory factors to medication errors have not been systematically synthesized yet. Thus, future systematic reviews should focus on these clinical areas such as oncology patients or outpatient and ambulatory settings.

This study has also identified the dearth of reviews incorporating theories in classifying contributory factors and developing interventions. This issue has been discussed before in the literature after some of the interventions that were implemented on a wide-scale have been proven ineffective or sometimes even had negative effect (238). The development of these interventions was based mainly on a pragmatic approach or ISLAGIATT (It Seemed Like A Good Idea At The Time) principle which lack the theoretical basis at the design stage (50, 238-242). The first crucial step to prevent an undesirable event is to explore and diagnose the behaviors and mediating pathways leading to it, which in this case would be contributory factors. This could be achieved through the explicit use of behavioral theories (239, 243). Accordingly, it is strongly encouraged that future researchers utilize behavior theoretical frameworks, such as the Theoretical Domain Framework (TDF), for both understanding contributory factors and developing

interventions that address these factors (244). Undertaking research utilizing theoretical frameworks can be a substantial undertaking. However, in the long run, such interventions have the potential to deliver important influence on medication errors.

Given the range of terminologies used to refer to contributory factors to medication errors, future research should utilize consistent terminology. Based on findings from this umbrella review, the consistent use of “contributory factors” is recommended. Although the term “causes” and “reasons” might be acceptable, it is advised to avoid their use. This is important to avoid confusion as these two terms have been used in different contexts in the literature. For example, some reviews represented fundamentally different concepts between “contributory factors” and “causes” (189, 245). Others used the terms “reasons” and “causes” interchangeably with “type” or “nature” of medication errors (32, 246).

It is pivotal to remove ambiguity and reach international consensus on all patient safety terminology, including contributory factors and its subclasses. This will enable the accurate quantification of the burden of each factor, analysis of data, and comparison of research outcomes (4, 21, 247, 248). It is also recommended to maintain consistency in the terms used across each study and to provide definitions for each term. This is of particular importance, as variation might lead to the inclusion of papers that may not actually be studying the phenomenon of interest. This could enhance the reliability of the outcomes and subsequently facilitate the development of possibly effective interventions.

Similarly, multiple definitions for contributory factors have emerged in the included reviews; however the summary presented in this thesis does not reflect all proposed definitions in the literature. Therefore, future research should focus on developing and

validating definitions of key terminologies used in research related to patient safety such as medication errors and contributory factors.

3.5 Conclusion

This umbrella review highlights a significant variation in terminology and definitions used to describe contributory factors in the published literature. Decision-making mistakes, which included failure to consider risk factors (e.g. chronic kidney disease and pediatrics) were the most common contributory factor, followed by factors related to the organization and environment such as understaffing and distractions. However, a lack of prespecified methodology to identify and classify contributory factors was noted. Additionally, none of the reviews evaluated the effectiveness of interventions to prevent errors.

The recommendations offered in this phase of the thesis have the potential to enhance consistency in the use of terminology, definitions, and methodology used in contributory factors to medication errors research. This will subsequently enable practitioners, policy makers, and other stakeholders to develop theory-informed interventions to promote patient safety. In addition, the comprehensive network of contributory factors synthesized in this review will inform future evaluations and classification of contributory factors and assist in the development of holistic interventions that target different levels of the healthcare system.

Chapter 4: prevalence, nature, contributing factors, and interventions to mitigate medication errors in outpatient and ambulatory settings: a systematic review

Phase two of this thesis will be reported in this chapter. An introduction to medication errors with focus on outpatient and ambulatory settings will be presented in the first section. This will be followed by the rationale and the aims of the study. Detailed methodology will also be reported, followed by the study findings with summary tables and figures. In the discussion, the results will be interpreted in context of other publications. Implications for policy, practice, and research will also be presented.

4.1 Introduction

Medication errors are common incidents across health systems that represent a serious public health problem posing a threat to patient safety (41). Several definitions are available in the literature and by patient safety bodies for medication errors. One of the most commonly adopted definitions is proposed by the National Coordinating Council for Medication Error Reporting and Prevention (NCCMERP) and it defines medication errors as “any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer” (10).

According to the World Health Organization (WHO), medication errors injure about 1.3 million people annually and cause at least one death daily in the Unites States (US) alone (249). These errors have also been linked to avoidable expenses. A systematic review published in 2017 showed that the cost of one error for healthcare systems ranged between €2 and €111 727 (46). Furthermore, the expenditure of error-induced morbidity and mortality for health systems exceeded $177.4 billion in one year in the US ambulatory care alone (250). Hence, improving medication safety have been declared by the WHO as the third global health and research priority (101).

Outpatient and ambulatory settings are defined as medical settings that provide general or specialized services that do not warrant hospital admission (79, 80). These settings have particular advantages in relation to minimizing admission-related complications and costs while maintaining the same level of care to inpatient settings (84, 85, 251). Furthermore, high-quality outpatient and ambulatory services lead to a meaningful enhancement in health and humanistic outcomes including increase patient satisfaction, promote prophylactic healthcare, provide sustainable management of chronic diseases, reduce unplanned doctor visits and hospitalization, and reduce mortality (87-92, 104). Therefore, establishment of outpatient settings has been prioritized by many healthcare systems in recent years alongside integrated models with primary care services (251, 252). The introduction of technological innovations has also permitted diagnostic and interventional procedures to be performed without hospitalization thereby expanding the role of outpatient and ambulatory settings (84, 85, 251).

Recent studies from the US and the United Kingdom (UK) highlighted that the prevalence of medication errors in outpatient and ambulatory sectors is high (41, 97, 98). For instance, the National Health Service (NHS)-England reported that four of every ten errors take place in ambulatory settings. Moreover, around three quarters of the 66 million clinically important medication errors that occur annually were in outpatient and ambulatory settings (41). Although this variation could be due to within-study factors such as the comparatively higher healthcare encounters occurring in outpatient and ambulatory settings or the tendency to report errors, contributory factors unique to this setting are worth investigating (96-98).

Whilst multiple systematic reviews have explored the rates, nature, and contributory factors to medication errors in a wide range of inpatient settings (32, 72, 106, 107, 253), synthesis of evidence from outpatient and ambulatory settings is missing. There is a rising demand for healthcare policy to manage patients in these settings to minimize healthcare costs and resources; and enhance patient access to services (252). Therefore, the aim of this review is to synthesize the peer-reviewed literature on the prevalence, nature, contributory factors, and interventions to minimize medication errors in outpatient and ambulatory settings. Findings from this review could enable policy makers to estimate the extent of the problem; understand the nature of these errors; and design effective interventions targeting the identified contributory factors.

4.2 Methods

4.2.1 Methodology reporting and registration

The reporting of this systematic review was conducted in accordance with the recommendations by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, to ensure inclusion of relevant information (133). The research protocol was registered with PROSPERO, the international prospective register of systematic reviews (appendix 4)— CRD42021291006 (254).

4.2.2 Eligibility criteria

Studies were considered for inclusion if they met the following criteria:

Domain:

For the purpose of this systematic review, the NCCMERP definition of medication errors (refer to section 1.1) was adopted. The definitions of medication errors employed by each study were also captured.

Participants:

Adult patients (≥18-year-old) managed in hospital-based outpatient clinics or ambulatory care facilities. No restriction on gender or clinical specialty was imposed.

Intervention(s):

The current review is not assessing a particular intervention and its impact on medication errors; thus the presence of a certain exposure is not a requirement for inclusion.

Comparator(s):

The current review is not assessing a particular intervention and comparing it to usual care or another comparator; thus the presence of a certain comparator is not a requirement for inclusion. For studies that compared outpatient and ambulatory settings to other settings (if any), only findings for outpatient and ambulatory settings will be extracted.

Outcomes:

Studies will only be included if they reported on the prevalence or contributory factors to medication errors in outpatients and ambulatory settings. Outcomes of interests include quantitative or qualitative outcomes related to the following:

1- Prevalence of medication errors in outpatient and ambulatory settings
2- Classification of medication errors according to the stage of the medication use process: prescribing, transcribing, administration, dispensing, and monitoring
3- Classification of medication errors according to incident type: not indicated, allergic reaction, wrong labeling, wrong quantity, patient self-administered error, incorrect patient, duplicate therapy, contraindication, wrong/omitted verbal patient direction, wrong dose/strength, wrong drug, and missed drug/omission (35).
4- Contributory factors to medication error
5- Characteristics and effectiveness of interventions proposed/implemented to reduce medication errors

Type of studies:

Any study design (e.g. observational studies, randomized controlled trials, qualitative studies) could be included on condition that the study reported on the prevalence or contributory factors.

Period:

Published in the last ten years (2011 onwards). Literature older than 10 years were not considered as the adoption of technology in healthcare in recent years was deemed to outdate prevalence data from older reports (84, 85).

Exclusion criteria: the following exclusion criteria were applied: (1) non-English language publications; (2) pediatric patients; (3) studies that exclusively focused on potentially inappropriate medications in the elderly population as they are not classified as medication errors; (4) editorials, commentaries, reviews, case-studies, and conference abstracts.

4.2.3 Data sources and search strategy

To identify eligible articles, a systematic literature search was undertaken using the following electronic bibliographic databases and search engines from 2011 until 2 November 2021: Medline, Embase, Cumulative Index to Nursing and Allied Health Literature (CINAHL), and Google Scholar (first 500 records). A summary of these databases is provided in section 3.2.3. Reference lists of included articles were also manually checked to locate any potentially relevant studies that were not yielded through the database search.

The search was carried out using Medical Subject Headings (MeSH) terms and keywords which were combined with Boolean operators 'AND' to combine terms of different categories and 'OR' to combine terms within one category. Table 4.1 summarizes the truncation and phrase searches used for the search strategy. The detailed search strategy and search terms for each database are available in appendix 5.

Table 4. 1 Search terms for phase two (systematic review)

Category	Search terms
Medication errors	medication error [MeSH] OR ((medication* OR transcrib* OR prescrib* OR dispens* OR administ*) adj3 (incident* OR mistake* OR error*))
Setting	outpatient clinics, hospital [MeSH] OR ambulatory care [MeSH] OR ambulatory care facilities [MeSH] OR outpatients [MeSH] OR ((ambulatory OR outpatient*) adj3 (care* OR healthcare* OR clinic* OR service* OR department* OR center* OR facilit*))

4.2.4 Study selection

Database hits and references identified from reference screening were transferred to EndNote 20® (2021 Clarivate) to remove duplicates. The remaining articles were imported into Rayyan Qatar Computing Research Institute (QCRI) software for the titles and abstracts screening (167). This was followed by full papers screening using Microsoft Excel. Screening was conducted by two independent reviewers (LN, VP or DS). In cases of disagreement, consensus was sought through discussion between the research team members.

4.2.5 Data extraction

Two reviewers (LN and VP) conducted the data extraction of five randomly selected studies to ensure consistency in the process. The data extraction for the remaining

studies was conducted by one reviewer (LN) and verified by a second reviewer (VP). A data extraction form was created through discussion between two reviewers (LN, VP), then piloted on five randomly chosen included studies.

The final data extraction sheet (appendix 6) included: authors, year of publication, country, setting, aim, duration, study design, participant sampling and recruitment, total number of participants/prescriptions, population/data characteristics, intervention characteristics (if any), methodology specific to prevalence data, duration for which prevalence data were collected, number of overall medication errors, and limitations (if any). The total number of observations (denominator) was also extracted. This could vary among studies, and it includes the total number of medications, the total number of patients, and the total number of prescriptions (which could contain more than one medication).

Additionally, the type of medication errors according to the medication use process stage (prescribing, transcribing, dispensing, administering, and monitoring), the type of prescribing errors (if any), and the number of errors in each stage/type were also extracted. A pre-specified list of the prescribing error types was adopted from a previously published paper with modification to fit the purpose of this study (35). A final list was generated and agreed upon after discussion with the research team (section 4.2.2). In the case of emerging recurring event, a new category was added.

For studies reporting on the severity of medication errors, methodology specific to severity classification, severity classes, and number of errors for each class were extracted.

For studies reporting on interventions to reduce medication errors, the following items were extracted: characteristics of the intervention, number of medication errors before and after implementing the intervention, total number of interventions or preventable errors, methodology for intervention subclassification (if any), intervention subclassification (if any), and acceptance rate.

Contributory factors were classified into two broad categories, active failure, and latent conditions. Active failures were further grouped into slips, lapses, mistakes, and violations.

4.2.6 Risk of bias

Two reviewers (LN and VP) assessed the quality of five randomly selected studies to ensure consistency in the process. The quality assessment for the remaining studies was conducted by one reviewer (LN) and verified by a second reviewer (VP). For studies reporting prevalence data, the quality assessment checklist for prevalence studies was used (255). This is a 10-question tool, with the last one being an overall risk of bias score. The items are: (1) Was the target population a close representation of the national population? (2) Was the sampling frame a true or close representation of the target population? (3) Was some form of random selection used to select the sample, or was a census undertaken? (4) Was the likelihood of non-response bias minimal? (5) Were data collected directly from the subjects (OR proxy)? (6) Was an acceptable case definition used? (7) Was the instrument that measured the parameter of interest shown to have reliability and validity (if necessary)? (8) Was the same mode of data collection used for all subjects? (9) Were the numerator(s) and denominator(s) for the parameter of interest

appropriate (10) Overall risk of bias expressed out of a total score of 9 points. Studies are considered of low risk if the final score was 0-3 points, moderate if the score was 4-6, and high risk if the total score was 7-9.

In case of studies with other designs were included, the intention was to use the Critical Appraisal Skills Programme (CASP) checklist as required according to the study design (256); however all included studies were suitable to be critically appraised according to the quality assessment checklist for prevalence studies.

4.2.7 Data synthesis and statistical analysis

A narrative approach to data synthesis was employed for data related to classification, nature, and contributory factors to medication errors. Data related to contributory factors were synthesized using the Reason's Accident Causation Model (described in section 1.5.2) (65). This model was chosen as it emphasizes on the systemic environment influence on accident causation phenomenon; hence it provides a comprehensive approach to understanding the factors contributing to medication errors that take place at any level of the system. This is believed to nudge preventative strategies towards paths that will yield better outcomes (63).

Simple linear models (described in section 1.5.2) were not used in this review as they cannot accommodate the complexity of healthcare systems (58, 62). The research team also preferred using Reason's theory over complex non-linear models (described in section 1.5.3), even though the latter could offer a deeper understanding of more complex systems, as the aim of these frameworks is to describe rather than predict and explain the factors contributing to a phenomenon (57, 73, 75). Thus, Reason' theory was believed

to be the best fit for this review as it will provide sufficient information about contributory factors to direct future interventions aimed at reducing medication errors.

Meta-analysis was planned for the following categories of data: (1) overall medication errors; (2) prescribing errors; (3) dosing errors; (4) wrong/suboptimal drug errors; (5) errors in relation to duration of use; and (6) errors in relation to frequency of prescribed medications. However, due to the high level of clinical and methodological heterogeneity, meta-analysis was not appropriate. Instead, statistical analyses without pooling were carried out. For interventional studies that reported the number of medication errors pre and post intervention [only one study (257) included in this review], pre intervention counts were included in the analysis. For proportions, the 95% confidence intervals were calculated using exact Binomial methods. For rates, the 95% confidence intervals were calculated assuming a Poisson distribution for events and normality was assumed on the natural log-rate scale. Statistical analyses were carried out with Stata version 16 Statistical Software (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC) by a statistician (MP).

4.3 Results

4.3.1 Study selection

A total of 1316 unique titles were screened, of which 24 fulfilled the inclusion criteria. The overall workflow of the records selection process is shown in the PRISMA flowchart (Figure 4.1). The reasons for excluding articles during the full text screening are presented in appendix 7 (Table 2).

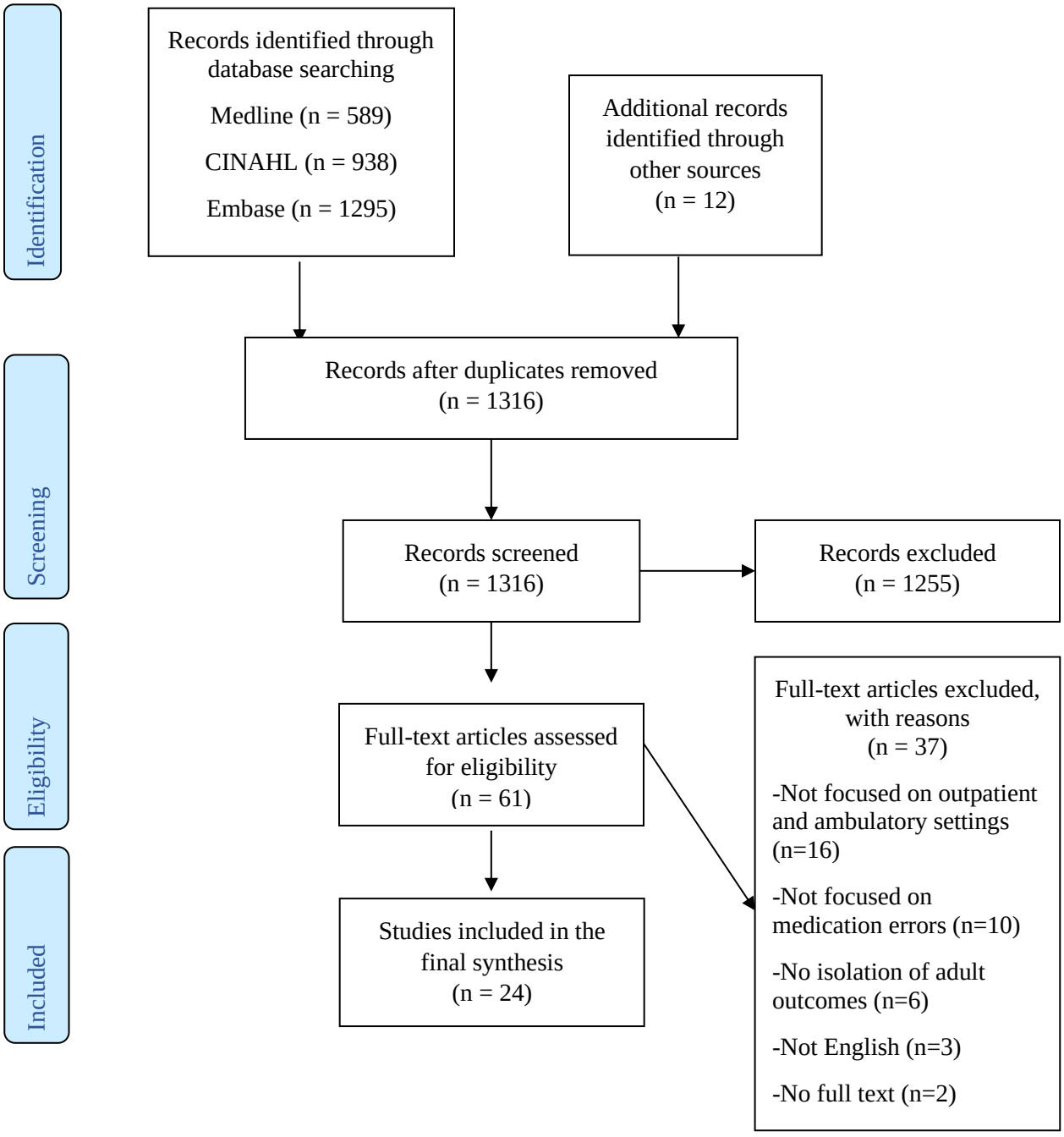

Figure 4. 1 PRISMA flow diagram of the study selection process for phase two (systematic review)

4.3.2 Characteristics of included studies

The characteristics of included studies are presented in Table 4.2. Of the 24 included studies, six were conducted in the US (257-262), four in India (263-266), and two each in Saudi Arabia (267, 268) and Brazil (267-270). One study was conducted in each Jordan (271), France (272), Puerto Rico (273), South Korea (274), Singapore (275), Ethiopia (276), Nigeria (277), Iran (278), Pakistan (279), and Nepal (280). Thirteen studies were prospective or retrospective cohort studies (260, 262, 264, 266-268, 270, 272, 273, 275-277, 279) and eleven were cross-sectional studies (257-259, 261, 263, 265, 269, 271, 274, 278, 280). The studies' follow-up duration ranged from 15 days (260) to 4 years (273).

Most studies (n=18) recruited participants from outpatient clinics (258, 260-266, 268-272, 275-280), while six were from ambulatory centers (257, 259, 267, 273-275). Although most studies (n=13) did not focus on a particular medical subspeciality, eleven focused exclusively on a single pharmacological class (e.g. opioids) or disease state (e.g. heart failure) (Table 4.2). Of these, three studies each incorporated chemotherapy (269-271) and cardiovascular diseases/medications (261, 262, 276); two each covered antimicrobial drugs (265, 277) and analgesics (260, 279); and one focused on three selected drug categories (274).

Among studies that did not focus on a particular subspeciality, six reported on agents frequently associated with medication errors. Four studies reported that cardiovascular drugs (including hypertension and dyslipidemia medications) were among the classes commonly associated with errors (257, 272, 273, 275). Gastrointestinal drugs (263, 272),

antimicrobials (257, 275), vitamins (258, 263), and analgesics (257, 263) were reported as the most common drug classes associated with errors in two studies each.

Throughout the studies, several potential denominators have been used to report prevalence data, this included patients (n=19), medicines (n=12), prescriptions (n=11), chemotherapy cycles (n=2), pharmaceutical consultations (n=1), and healthcare procedures (n=1). For the purpose of the statistical analyses, authors of seven studies were contacted to clarify their use of terminology (e.g. if they used prescriptions and medications interchangeably). Among those who were contacted, the denominators were confirmed for five studies.

Table 4. 2 Study characteristics (n=24)

Author, year of publication	Country, setting	Aim	Duration	Study design	Participants sampling and recruitments, total number of participants	Total number of observations (denominator)	Population/ data characteristics	Study outcomes	Medication most frequently attributed with ME
Abramson E, 2011 (257)	USA, ambulatory care centers	To determine the rates and types of PE among paper-based, primary care prescribers in solo and small group practices in two communities, and to determine the potential impact of e-prescribing on these errors	15 months	Non-randomized cross-sectional study	All prescriptions written by participating providers during a 2-week period were evaluated, ensuring that we obtained at least 75 prescriptions on 25 patients per provider and extending data collection if necessary. Prescription review was limited to three randomly selected prescriptions per patient to minimize clustering of errors	5955 patients (9385 prescriptions)	New York: Mean age: 54 years (SD 17), Female: 2388 (63%) Massachusetts: Mean age: 51 years (SD 18), Female: 1324 (62%)	-PE -Types of PE -Intervention outcomes -Contributory factors	-Antibiotics: 1516 (16.4%) -Dyslipidemia drugs: 530 (5.7%) -Narcotics: 500 (5.4%)
Abramson E, 2013 (258)	USA, outpatient clinic	To assess the rates and types of PE 2 years after transition to an Electronic Health Record (EHR) with robust clinical decision support (CDS) and determine	3 months	Mixed methods cross-sectional case study	Electronic prescriptions were extracted from the electronic health records database for a 2-week period. Prescriptions written by residents were excluded	920 patients (1905 prescriptions)	Mean age: 57 years (SD 16), Female: 632 (69.2%)	-PE -Types of PE -Contributory factors	-Vitamins: 9 (12.7%) -Inhaled bronchodilators: 5 (7.0%) -Antihistamines: 4 (5.6%)

		the evolution of errors							
Al Khawaldeh T, 2017 (271)	Jordan, hematology and oncology outpatient departments at 2 hospitals	To describe types, frequencies and stages of errors which occurred during administration of commonly used intravenous (IV) cancer chemotherapy medications inclusive of “aseptic technique"	6 weeks	Prospective cross-sectional study	NR	334 drugs administered/ prescriptions	NR	-Administration errors -Contributory factors	-Study focused on IV chemotherapy only
Al-Khani S, 2013 (267)	Saudi Arabia, ambulatory care setting	To explore factors that help pharmacists identify and thus prevent harm from incorrect drug PE in an ambulatory care setting	21 months	Retrospective study	All prescribing errors reported during the duration of the study were included	NR	NR	-PE -Types of PE -Contributory factors	NR
Assiri G, 2019 (268)	Saudi Arabia, family medicine clinics	To investigate the period prevalence and risk factors for clinically important prescription and monitoring	18 months	Retrospective cohort study	Several ambulatory care centers were contacted for fieldwork selection. Family Medicine clinics in two hospitals were selected. A random sample of patients visiting the family	2,000 patients	Mean age: 49.9 years, Female: 1,302 (65.1%), Polypharmacy: 1,115 (55.8%)	-Overall clinically important ME -ME according to the use process	NR

		errors among adults managed in community care in Saudi Arabia			medicine clinics was generated			-Types of PE - Contributory factors	
Belaiche S, 2012 (272)	France, outpatient nephrology clinics at a university hospital	To assess the impact of clinical pharmacy services in outpatient nephrology clinics	15 months	Retrospective study	All patients seen by the clinical pharmacist during the study duration but analyzed the data of only those patients seen more than twice, so as to observe any benefit from the introduction of pharmaceutical care	42 patients (350 pharmaceutical consultations, 287 drugs)	Mean age: 64.9 years (SD 2.2), Female: 21 (50%), Stage 4 CKD: 17 (40.5%), Stage 3 CKD: 16 (38.1%), Mean number of drugs: 8.6 (SD 0.6)	-Overall ME -ME according to the use process -Types of PE -Intervention outcomes - Contributory factors	- Cardiovascular drugs: 95 (33.1%) - Gastrointestinal drugs: 82 (28.6%) -Blood and blood derivatives: 62 (21.6%)
Bell S, 2020 (259)	USA, 3 healthcare organizations including 79 ambulatory care practices	To assess the frequency and types of errors identified by patients who read open ambulatory visit notes	5 months	Survey study	NR	22,889 patients	Mean age: 55.16 years (SD 15.96), Female: 14 447 (63.1%)	-Overall serious ME - Contributory factors	NR
Bicket M, 2018 (260)	USA, outpatient departments at a tertiary medical center	To determine opioid prescribing patterns and rate of three types of errors, discrepancies, and variation	15 days	Retrospective study	All opioid medication prescriptions received and processed by one outpatient pharmacy for 15 consecutive days	451 patients (510 prescriptions)	Mean age: 47.5 years (SD 17.4), Handwritten prescriptions: 234 (47%), Hospital computer-	-Overall ME - Contributory factors	-Study focused on opioids only - Tablet form: 92%

		from ideal practice					generated: 234(47%)		
Carollo J, 2017 (269)	Brazil, outpatient chemotherapy unit of a teaching hospital	To identify medication related incidents in outpatient chemotherapy unit of a teaching hospital	3 months	Cross-sectional and descriptive study	The calculation of minimal sample to develop the study was based on 12,778 health care procedures done in 2015. Recruitment not mentioned	1,403 patients (1,403 healthcare procedures)	Mean age: 57.6 years (SD 15.2), Female: 819 (58.4%)	-Overall ME -ME according to the use process -Types of PE -Severity classification -Contributory factors	-Study focused on chemotherapy only -IV route of administration : 680 (48.5%)
Dempsey J, 2017 (261)	USA, heart failure subspecialty clinic, or Ambulatory Cardiac Triage, Intervention, and Education (ACTIVE) unit at Brigham and Women's Hospital	To describe the patient population served in the ACTIVE and to document the prevalence of comorbidities and ME to define the most effective role of a pharmacist in the unit	5 months	Cross-sectional study	Consecutive visits to the heart failure subspecialty clinic, or ACTIVE unit, that included pharmacist consultation	60 patients	Mean age: 69, Male: 36 (60%), Heart failure reduced ejection fraction (HFrEF): 39 (65%), Mean number of medications: 14	-PE -Types of PE -Intervention outcomes -Contributory factors	-Study focused on heart failure only -NR
Duarte et al, 2018 (270)	Brazil, outpatient oncology and chemother	To identify and quantify the interventions carried out in an outpatient	6 months	Prospective observational study	Prescriptions for all patients who were treated with chemotherapy during the study period were	780 patients (3526 prescriptions)	Mean age: 60.6years (SD 13.2), Female: 262 (33.64%)	-PE -Types of PE	-Study focused on chemotherapy only

	apy clinic at a university hospital	clinical oncology setting, to characterize the pharmacist's work and correlate it to the reduction in ME and increase in patient safety			delivered daily to the chemotherapy pharmacy service by the nursing staff and/or clinical staff			-Severity classification -Intervention outcomes -Contributory factors	
Hernández S, 2018 (273)	Puerto Rico, 330 ambulatory health care centers	To assess the incidence of ME, ADE, and poADE in patients 65 years of age and older	4 years	Observational retrospective cohort study	The study sample was selected by convenience in a nonrandomized selection from event reports completed in those years	2,218 patients	Mean age: 73.4 (SD 7.4), Female: 112 (65.9%), Mean number of medical conditions: 3.5 (SD 1.8), Mean number of medications: 6.8 (SD 3.9)	-Overall ME -ME according to the use process -Severity classification -Contributory factors	-Anticoagulants: p-value <0.001
Howard M, 2016 (262)	USA, family medicine, internal medicine, and geriatrics clinics	To identify patient- and process-related factors that correlate with increased risk of inappropriate prescribing in patients started on DOACs	6 months	Retrospective chart review	Patients were identified by the institution's electronic health record by having an active DOACs on their medication list for the study duration	167 patients (167 drugs/ prescriptions)	Mean age: 69.7 years (SD 15.5). Female: 68 (40.7%). Taking rivaroxaban: 105 (62.9 %). Indication of atrial fibrillation: 125 (74.9 %)	-Dosing errors -Contributory factors	-Study focused on DOACs only

Kim G, 2016 (274)	South Korea, 43 medical institutions with hemodialysis facility	To assess the quality of care for end-stage renal disease outpatients using their renal dosing adjustment status	3 months	Cross-sectional study	Out of the 527 centers with hemodialysis facility, 10% were selected by systematic sampling. Nurses in the centers filled out the questionnaire using patient medical records and hemodialysis data to recruit all patients who met the inclusion criteria	828 patients (1097 drugs)	Age 18-49: 230 (27.8%), age 50-59: 231 (27.9%), male: 497 (60%), GFR <10 mL/min/1.73 m2: 785 (94.8%), duration of hemodialysis 1-5 years: 376 (45.4%)	-Dosing errors -Contributory factors	-Study focused on 85 drugs in three classes: antihypertensives, antihyperglycemics and dyslipidemia drugs
Lee P, 2016 (275)	Singapore, kidney transplant ambulatory clinic	To evaluate the clinical pharmacy service in a post-kidney transplant ambulatory clinic in Singapore General Hospital	19 months	Prospective, observational study	All ME and medication discrepancies documented at the clinic during the study duration were retrieved from the system for analysis	1271 patients (3581 prescriptions)	NR	-PE -Types of PE -Intervention outcomes -Contributory factors	-Immunosuppressive drugs: 25.3% -Anti-infectives: 14.1% -Antihypertensive drugs: 12.0%
Niriayo Y, 2018 (276)	Ethiopia, ambulatory care heart failure clinic at a teaching hospital	To assess the prevalence and contributing factors of DTP among ambulatory heart failure patients in Jimma University	12 months	Prospective observational study	Patients were recruited during their appointment for medication refilling. A sample of 355 was calculated using a single population proportion formula assuming 50% proportion of ME	340 patients (1389 drugs)	Mean age: 50.5 years (SD 15.6), Female: 171 (50.3%), Rural area: 214 (62.9%), Not educated: 194 (57.1%), Mean comorbidities	-PE -Types of PE -Contributory factors	-Study focused on heart failure only -Beta-blockers: 34.4% -Angiotensin-converting-enzyme inhibitors

		Specialized Hospital					per patient: 1.9 (SD 0.9), New York Heart Association (NYHA) classes III: 165 (48.5%)		(ACEIs): 24.8% -Dyslipidemia drugs: 16.5%
Ojeh V, 2015 (277)	Nigeria, outpatient HIV clinic at a teaching hospital	To describe the frequency and types of DTP, and interventions carried out to resolve them, among a cohort of HIV- infected patients on ART	8 months	Prospective descriptive study	All HIV infected adults that presented at the pharmacy with prescription for routine ART pick up or initiation during the study duration	9,339 patients (42,416 prescriptions)	Mean age: 41 years (SD 10), Female: 6,817 (73%)	-PE -Types of PE -Intervention outcomes - Contributory factors	-Study focused on antiretroviral drugs only
Prasad D, 2020 (263)	India, outpatient general medicine department	To identify and intervene the prescribing and dispensing errors among the Outpatient General Medicine department	6 months	Cross sectional, interventional study	All patients who visited the clinic and met the inclusion criteria were collected randomly at the dispensing area in the pharmacy department	544 patients (544 prescriptions, 1768 drugs)	Age 41-50: 68 (22%), Female: 169 (56%), Diagnosis not mentioned: 73 (24.1%)	-Overall ME -ME according to the use process -Types of PE -Severity classification - Contributory factors	-Vitamins: 386 (21.8%) - Gastrointestinal drugs: 370 (20.9%) -NSAIDs: 307 (17.4)

Priya K, 2017 (264)	India, outpatients in a quaternary care hospital	To review the clinical benefits of pharmacist driven electronic prescription audit process in monitoring and detecting PE before it reaches the patient	12 months	Prospective study	NR	23,750 drugs	NR	-PE -Types of PE -Severity classification -Intervention outcomes -Contributory factors	NR
Rouhani M, 2018 (278)	Iran, two outpatient cancer centers	To evaluate the effects of the chemotherapy standard form and identify the rates and types of ME in relation to the early detection of toxicity and ADR in outpatients with breast cancer	6 months	Prospective, cross-sectional interventional study	All standard forms were collected, and ME and possible side effects were evaluated	84 patients (217 cycles, 385 drugs)	Breast cancer patients. Mean age: 46.17 years (SD 9.5). Female: 81 (96.4%)	-Overall ME -ME according to the use process -Types of PE -Contributory factors	NR
Shaikh A, 2017 (279)	Pakistan, outpatient departments in several hospitals and primary healthcare facilities	To compare the extent of PE in NSAIDs in different health care facilities of district Khairpur to improve rational prescribing and decrease cardiovascular	NR	Retrospective study	NR	479 prescriptions	Missing diagnosis: 402 (84%) prescriptions	-PE -Types of PE -Contributory factors	-Study focused on NSAID only

		and gastrointestinal problems associated with improper use of NSAID							
Shakuntala B, 2019 (265)	India, outpatient ophthalmology department at a tertiary hospital	To analyze the prescription of antibiotics used for infectious diseases in ophthalmology outpatient department (OPD)	4 months	Prospective, observational, and cross-sectional study	Adult patients of either sex who registered newly and visiting ophthalmology outpatient department for curable complaints were included in the study	900 patients (900 prescriptions, 1400 antibiotic)	Age 31-60: 423 (47%), Female: 378 (42%), Prescription with brand name: 1243 (88.8%), Eye drops: 966 (69%), Mean drugs/prescription: 2.62	-PE -Types of PE	-Study focused on antibiotics only -Fluoroquinolones: 1218 (87%) -Eye drops: 69%
Shrestha R, 2019 (280)	Nepal, outpatient departments at a district hospital	To understand the prescribing practices and errors, which will lead to developing a proper health care policy; which will, in turn, improve the quality of the use of medicine and healthcare facilities	2 months	Retrospective, cross-sectional, and quantitative study	The sample was selected using stratified (according to department) random sampling by dividing the sample number for each department based on the prescription number of each department	770 prescriptions, 2448 drugs	Mean drugs/prescription: 3.2, Prescriptions with antibiotic: 37.9%, Prescriptions with injection: 0.7%, Drugs prescribed by generic name: 2.9%	-PE -Types of PE -Severity classification -Contributory factors	NR
Thakur H, 2013 (266)	India, medicine department	To study the ME leading to noncompliance	5 months	Prospective	NR	100 patients	NR	-Overall ME	NR

	in a teaching hospital	in a tertiary care teaching hospital		cohort study					
ME: medication errors; PE: prescribing errors; SD: standard deviation; NR: not reported; CKD: chronic kidney disease; NSAID: non-steroidal anti-inflammatory drugs; ADE: adverse drug events; poADE: potential ADEs; DOAC: direct oral anticoagulants; DTP: drug therapy problem; ART: antiretroviral therapy									

4.3.3 Risk of bias

The overall quality of included studies was assessed to be moderate (Table 4.3): five studies were at low risk of bias, thirteen were at moderate risk, and six were at high risk. This was mainly due to potential biases with the recruitment and sampling procedures; however most studies sufficiently described their data collection process.

Table 4. 3 Quality assessment of included studies

Author, year of publication	Was the target population a close representation of the national population?	Was the sampling frame a true or close representation of the target population?	Was some form of random selection used to select the sample, OR, was a census undertaken?	Was the likelihood of non-response bias minimal?	Were data collected directly from the subjects (OR proxy)?	Was an acceptable case definition used?	Was the instrument that measured the parameter of interest shown to have reliability and validity (if necessary)?	Was the same mode of data collection used for all subjects?	Were the numerator(s) and denominator(s) for the parameter of interest appropriate	Overall risk of bias
Abramson E, 2011	No	No	Yes	No	Yes	Yes	Yes	Yes	Yes	3 (low risk)
Abramson E, 2013	No	No	No	No	Yes	Yes	Yes	Yes	Yes	4 (moderate risk)
Al Khawaldeh T, 2017	No	No	No	Yes	Yes	Yes	Yes	No	Yes	4 (moderate risk)
Al-Khani S, 2013	No	Yes	Yes	Yes	No	Yes	No	No	No	5 (moderate risk)
Assiri G, 2019	No	Yes	Yes	No	No	Yes	Yes	Yes	No	3 (low risk)
Belaiche S, 2012	No	Yes	No	No	Yes	No	No	No	No	3 (low risk)
Bell S, 2020	Yes	Yes	No	No	Yes	No	Yes	Yes	Yes	6 (moderate risk)
Bicket M, 2018	Yes	No	No	Yes	Yes	No	Yes	Yes	Yes	3 (low risk)
Carollo J, 2017	No	Yes	No	No	Yes	No	No	Yes	No	4 (moderate risk)
Dempsey J, 2017	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	5 (moderate risk)

Duarte N, 2018	No	No	No	No	Yes	Yes	No	Yes	Yes	4 (moderate risk)
Hernández S, 2018	No	Yes	No	Yes	Yes	No	No	Yes	No	4 (moderate risk)
Howard M, 2016	No	No	No	No	Yes	Yes	Yes	Yes	Yes	4 (moderate risk)
Kim G, 2016	No	Yes	No	No	No	Yes	Yes	Yes	Yes	2 (low risk)
Lee P, 2016	No	No	No	No	Yes	Yes	Yes	Yes	Yes	5 (moderate risk)
Niriayo Y, 2018	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	5 (moderate risk)
Ojeh V, 2015	No	No	No	No	Yes	Yes	No	Yes	Yes	7 (high risk)
Prasad D, 2020	No	No	Yes	No	Yes	No	No	Yes	Yes	7 (high risk)
Priya K, 2017	No	No	No	Yes	Yes	No	No	No	No	7 (high risk)
Rouhani M, 2018	No	No	No	No	Yes	No	No	Yes	Yes	7 (high risk)
Shaikh A, 2017	No	No	No	No	Yes	No	No	Yes	No	4 (moderate risk)
Shakuntala B, 2019	No	No	No	No	Yes	No	No	No	Yes	9 (high risk)
Shrestha R, 2019	No	Yes	Yes	Yes	Yes	No	No	Yes	No	3 (low risk)
Thakur H, 2013	No	No	No	No	No	No	No	No	No	6 (moderate risk)
Low risk of bias: final score 0-3 points; moderate risk of bias: final score 4-6; high risk of bias: final score 7-9										

4.3.4 Methods and resources used to identify and validate medication errors

Twenty studies provided descriptions, in various levels of details, about the approaches used to obtain prevalence data. Reviewing prescriptions/patients' records was the predominant method (257-262, 264, 265, 268-270, 273, 274, 280). Pharmacists were the professionals mostly performing these revisions, followed by nurses, physicians, and multidisciplinary teams. Other methods included pharmaceutical consultations (272, 275-277), direct observation (271), and reviewing medication errors reports (267). Ten studies briefly described the instruments/standards used to identify medication errors (257-260, 268-270, 276, 279, 280). Eight studies conducted validation of outcomes, for which double checking or consensus were used (257, 261, 267, 268, 272, 273, 275, 276). Only four studies had uniform training of the individuals involved in the identification and verification processes (257, 258, 276, 280).

4.3.5 Prevalence of medication errors without associating them with the stages of the medication use process

The rate of overall medication errors was investigated in nine studies (Table 4.4), of which one study focused on "clinically important" medication errors (268) and another one on "serious" medication errors as reported by patients (259). The latter two studies did not provide a definition for clinically important and serious errors; however Assiri et al (2019) reported that they adapted a previously published definition.

The proportion of prescribed drugs associated with medication errors ranged between 23%-92% in the three studies that used the total number of drugs as a reporting unit (Figure 4.2). In the five studies that used the number of patients as a reporting unit, the

rate of errors per patient ranged from 1.06 to 6.26 (appendix 8, figure 1). The rate of clinically important medication errors per patient was 0.08 in family medicine clinics (268), while patients attending general ambulatory practice reported 50 serious medication errors (14% of the overall observed errors) in a pool of 22,889 patients (259). It is worth noting that the latter study evaluated patient-reported errors and that the study did not solely focus on medication errors (e.g. physical examination errors were included) (259).

The proportion of prescriptions (contains more than one drug) with at least one medication error ranged between 42% and 56% in two studies (260, 263). In a further study that focused on older adults, the incidence rate of medication errors was found to be 12.5 per 100 person-years (95% CI 9.4-16.2) (273).

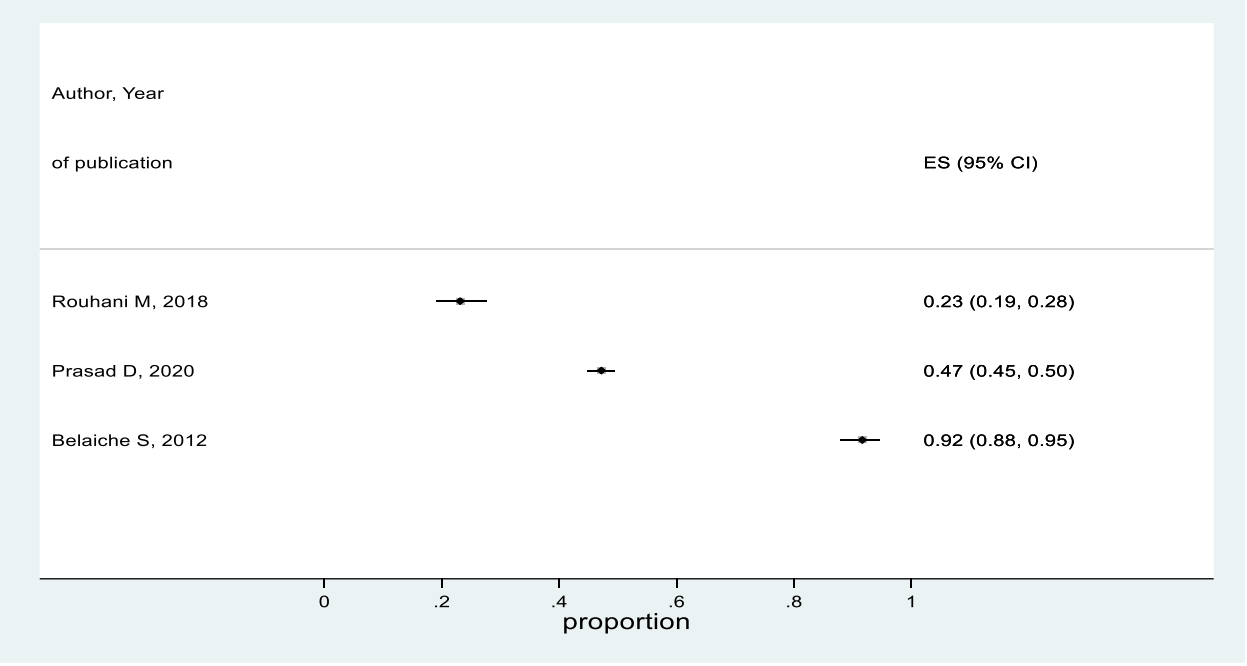

Figure 4. 2 Forest plot of medications with errors as a proportion of total medications

Table 4. 4 Outcomes of studies reporting on the prevalence of overall medication errors (n=9)

Author, year of publication	Methodology specific to prevalence data	Duration of prevalence data collection	Total number of observations (denominator)	Number of overall ME
Assiri G, 2019 (268)	In-depth electronic record screening, involving the assessment of diagnostic, medication list, and laboratory data, was conducted. Clinically important errors in medicine management, as defined by the PINCER trial were identified. A second trained reviewer undertook the independent assessment of a random 10% of the sample of records. Any discrepancy was discussed and resolved through double checking of records or arbitration if a decision could not be reached	15 months	2,000 patients	162 patients with clinically important errors
Belaiche S, 2012 (272)	Pharmaceutical consultations by the pharmaceutical team (1 senior clinical pharmacist and 1 clinical pharmacy resident)	15 months	42 patients (350 pharmaceutical consultations, 287 drugs)	263 ME
Bell S, 2020 (259)	Survey was adapted from the OpenNotes questionnaire. To help focus patients on their notes, the survey included a screenshot of the location of notes on each organization's patient portal. The survey included 4 questions about mistakes. Included Likert scale, yes/no, multiple choice questions, and open-ended questions	5 months	22,889 patients	50 serious ME
Bicket M, 2018 (260)	One investigator examined prescriptions for errors according to three standards: 1) PE based on "best practice" guidelines; 2) The Joint Commission recommendation for two patient identifiers; and 3) the DEA Practitioner's Manual Valid Prescription Requirements. A second investigator independently examined a subset of handwritten prescriptions and prescriptions noted to contain at least one error for confirmation. Any discrepancies were resolved by consensus	15 days	451 patients (510 prescriptions)	214 prescriptions contained at least one error
Carollo J, 2017 (269)	Data was collected using an instrument divided into four sections by evaluating patients' medical records who received care, technical complaints forms and incident notifications	3 months	1,403 patients (1,403 healthcare procedures)	4867 ME
Hernández S, 2018 (273)	The necessary data to evaluate the incidence of ME were obtained from reports, medical records review, and pharmacy dispensing medication profiles. A pharmacy student performed the data collection and records review under supervision of a	4 years	2,218 patients	93 ME

	clinical pharmacy preceptor and the pharmacy department director, both Doctors of Pharmacy			
Prasad D, 2020 (263)	NR	6 months	544 patients (544 prescriptions, 1768 drugs)	834 ME
Rouhani M, 2018 (278)	NR	6 months	84 patients (217 cycles, 385 drugs)	89 ME
Thakur H, 2013 (266)	NR	5 months	100 patients	171 ME
ME: medication errors; NR: not reported				

4.3.6 Prevalence of medication errors according to the medication use process

Of the 24 studies included in this systematic review, 18 reported on prescribing errors, five on administration errors, three on dispensing errors, one on monitoring errors, and none on transcribing errors (Table 4.5).

A wide range of prevalence of prescribing errors was reported with errors ranging from 0-91% of all medications prescribed (Figure 4.3), while the rate of prescribing errors per patient ranged between 0 and 6.21 in 13 included studies (appendix 8, figure 2). Among studies that reported denominators other than patients and medications, 156 (7.8%) prescriptions were found to have clinically important prescribing error in 2000 patients attending family medicine clinics (268). Another study focused only on nonsteroidal anti-inflammatory drugs (NSAIDs) and reported 458 prescribing errors in 479 prescriptions (279). Al-Khani et al (2013) reported 2073 prescribing errors; however this study did not report a denominator (267).

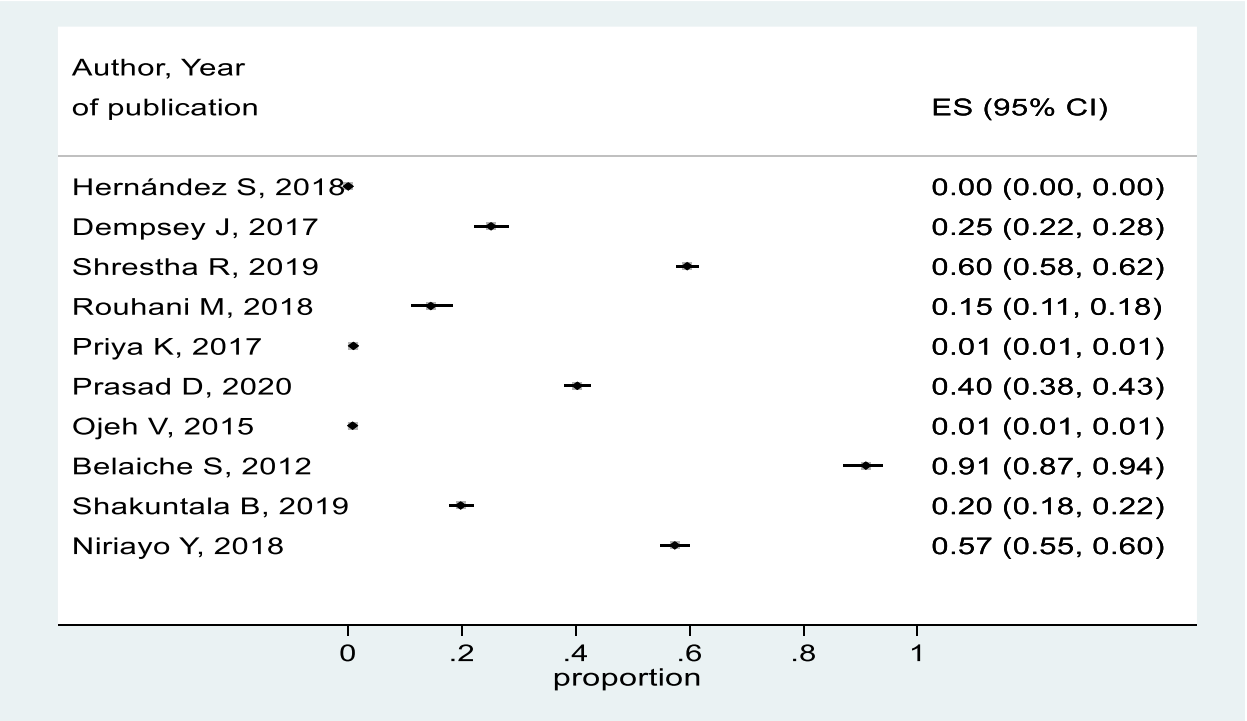

Figure 4. 3 Forest plot of medications with prescribing errors as a proportion of total medications

Among studies reporting administration errors (n=5), four used the total number of patients as a denominator. The proportion of patients with errors in these studies ranged from 0% (273) to 39.2% (278). One study had 654 administration processes, projecting 15,042 opportunities for error, of which 4112 (27.3%) errors were detected (271). This study focused on intravenous (IV) chemotherapy only and defined administration errors as any deviation from hospital protocol, which also incorporated aseptic techniques (271).

Dispensing errors were assessed in three studies. The first study focused on chemotherapy and detected 21 (1.5%) dispensing errors in 1403 patients (269). The second study recruited elderly patients (≥65 year-old) and had an incident rate of 20.7

per 100 person-years (273) whilst the third, reported 122 (22.4%) errors in 544 patients (263).

Only one study reported monitoring errors, with six (0.3%) clinically important errors in a pool of 2,000 patients. One high-risk error was identified due to the lack of lithium level follow-up for more than 3 months (268).

Table 4. 5 Outcomes of studies reporting prevalence data according to the medication use process and type of prescribing errors

Author, year of publication	Methodology specific to prevalence data reported according to the use process	Methodology specific to classifying ME according to the type of prescribing error	Duration of prevalence data collection	Total number of observations (denominator)	Number of errors according to the medication use process	Number of errors according to the type of prescribing errors
Abramson E, 2011 (257)	A physician trained a nurse and pharmacist in an identical manner using well-used, standardized methodology. Interrater reliability was determined by having the pharmacist and nurse evaluate the same random sample of 2% of the data and calculating the k score for agreement	Errors classified in accordance with definitions from the Institute of Medicine	2 weeks	5955 patients (9385 prescriptions)	-PE: 19,956	-Wrong dose/strength: 736 -Wrong frequency: 192 -Wrong duration: 333 -Wrong/omitted patient direction: 394 -Others: 18,301
Abramson E, 2013 (258)	An experienced nurse reviewer evaluated all prescriptions. This nurse had previously been trained to apply extensively used and standardized methodology that also includes error classification and identification	Errors classified in accordance with definitions from the Institute of Medicine	2 weeks	920 patients (1905 prescriptions)	-PE: 71	-Wrong dose/strength: 8 -Wrong frequency: 17 -Wrong duration: 5 -Wrong/omitted patient direction: 7 -Wrong route: 1 -Others: 32
Al Khawaldeh T, 2017 (271)	The researcher (clinical pharmacist) undertook direct observation of 5 outpatient nurses who administered chemotherapy drugs	Not studied	6 weeks	334 drugs administered/ prescriptions	-Administration errors: 965	Not studied
Al-Khani S, 2013 (267)	All PE reported to the electronic reporting system (voluntary) by the pharmacist and reviewed by the quality control department and medication safety officer. Reports were thoroughly reviewed and evaluated by two researchers	Errors classified in accordance with the classification of the electronic reporting system	21 months	NR	-PE: 2073	-Wrong dose/strength: 1099 -Wrong/suboptimal drug: 242 -Wrong frequency: 180 -Wrong duration: 49

						-Wrong route: 30 -Other: 473
Assiri G, 2019 (268)	In-depth electronic record screening, involving the assessment of diagnostic, medication list, and laboratory data, was conducted. Clinically important errors in medicine management, as defined by the PINCER trial were identified. A second trained reviewer undertook the independent assessment of a random 10% of the sample of records. Any discrepancy was discussed and resolved through double checking of records or arbitration if a decision could not be reached	NR	15 months	2,000 patients	-Clinically important PE: 156 -Clinically important monitoring errors: 6	-Wrong/suboptimal drug: 33 -DDI: 2 -Combination of errors: 34 Other: 87
Belaiche S, 2012 (272)	Pharmaceutical consultations by the pharmaceutical team (1 senior clinical pharmacist and 1 clinical pharmacy resident)	NR	15 months	42 patients (350 pharmaceutical consultations, 287 drugs)	-PE: 261 -Administration errors: 2	-Wrong dose/strength: 116 -Wrong/suboptimal drug: 19 Others: 126
Carollo J, 2017 (269)	Data was collected using an instrument divided into four sections by evaluating patients' medical records who received care, technical complaints forms, and incident notifications	NR	3 months	1,403 patients (1,403 healthcare procedures)	-PE: 4819 -Dispensing errors: 21 -Administration errors: 27	-Wrong dose/strength: 457 -Wrong/suboptimal drug: 480 -Wrong duration: 529 -Wrong rout: 21, -Others: 3,332
Dempsey J, 2017 (261)	A pharmacist reviewed each patient's medical profile and medication list to identify and categorize ME. Each documented ME was verified by a second pharmacist	Errors classified in accordance with the drug-related problems described by Hepler and Strand	5 months	60 patients	-PE: 211	-Wrong dose/strength: 26 -Wrong/suboptimal drug: 46 -DDI: 90 -Contraindication: 11 -Others: 38

Duarte et al, 2018 (270)	A pharmacist evaluated prescriptions according to a set criteria such as using treatment protocol and dosage calculations	NR	6 months	780 patients (3526 prescriptions)	-PE: 220	-Wrong dose/strength: 79 -Wrong/suboptimal drug: 58 -Wrong frequency: 4 -Wrong duration: 2 -Others: 77
Hernández S, 2018 (273)	The necessary data to evaluate the incidence of ME were obtained from reports, medical records review, and pharmacy dispensing medication profiles	Not studied	4 years	2,218 patients	-PE: 7 Dispensing errors: 86 -Administration errors: 0	Not studied
Howard M, 2016 (262)	Not studied	Appropriateness of initial dose was determined by the investigators at the time of data collection. The term “appropriate dose" was defined, and it complies with FDA approved doses	6 months	167 patients (167 drugs/ prescriptions)	Not studied	-Wrong dose/strength: 24
Kim G, 2016 (274)	Not studied	Two clinical pharmacists reviewed the prescription data and evaluated the adherence to renal dosing recommendations based on each patient’s eGFR in accordance with Micromedex or Lexicomp	40 days	828 patients (1097 drugs)	Not studied	-Wrong dose/strength: 452

Lee P, 2016 (275)	At each visit, the patient was seen by the transplant pharmacist after consultation with the physician. The pharmacist reviewed and optimized the medication regimens. Any ME or discrepancies identified during the consultation were discussed with the physicians-in-charge	Errors classified in accordance with the Strand criteria and American College of Clinical Pharmacy guidelines for therapeutic interchange	19 months	1271 patients (3581 prescriptions)	-PE errors: 843	-Wrong dose/strength: 254 -Wrong/suboptimal drug: 75 -DDI: 3 -Others: 511
Niriayo Y, 2018 (276)	Patients were interviewed consecutively according to their appointment schedule using the interview questionnaire and their respective medical chart was retrieved using the retrieval checklist. Three clinical pharmacists, two nurses and one physician were involved in data collection. Training and orientation were given to professionals involved in data collection. ME were identified using the Cipolle's method followed by a consensus meeting with a panel of experts. The experts further refined ME identification method to the study setting based on treatment guidelines and literature reviews	Errors classified in accordance with the Cipolle's method followed by a consensus meeting with a panel of experts. The experts further refined ME classification method to the study setting based on treatment guidelines and literature reviews	12 months	340 patients (1389 drugs)	-PE: 800	-Wrong dose/strength: 259 -Wrong/suboptimal drug: 267 -Others: 274
Ojeh V, 2015 (277)	At every fill/refill visit, pharmacists engaged in face-to-face interaction with the patient to verify the accuracy of prescriptions with consideration to clinical and laboratory parameters	NR	8 months	9,339 patients (42,416 prescriptions)	-PE: 345	-Wrong dose/strength: 16 -Wrong/suboptimal drug: 110 -DDI: 6 -Contraindication: 2 -Others: 211
Prasad D, 2020 (263)	NR	NR	6 months	544 patients (544 prescriptions, 1768 drugs)	-PE: 712 -Dispensing error: 122	-Wrong dose/strength: 19 -Wrong/suboptimal drug: 75

						-Others: 618
Priya K, 2017 (264)	Pharmacists auditing e-prescriptions	PE classified in accordance with the NCCMERP guidelines. In addition to pharmacist own professional knowledge, other clinical guidelines like UpToDate and PubMed journals	12 months	23,750 drugs	-PE: 226	-Wrong frequency: 78 -DDI: 56 -Other: 6
Rouhani M, 2018 (278)	NR	NR	6 months	84 patients (217 cycles, 385 drugs)	-PE: 56 -Administration errors: 33	-Wrong dose/strength: 34 -Others: 22
Shaikh A, 2017 (279)	Identifying errors as per the WHO prescription writing guidelines, authenticated drug references drug information book and the British National Formulary (BNF)	NR	NR	479 prescriptions	-PE: 458	-Wrong dose/strength: 112 -Wrong frequency: 9 -Wrong duration: 44 -Wrong route: 89 -DDI: 92 -Others: 112
Shakuntala B, 2019 (265)	The required information recorded prospectively in a specially designed form (case record/report form) from the outpatient department prescription letter of every patient in the study	NR	4 months	900 patients (900 prescriptions, 1400 antibiotic)	-PE: 277	-Wrong frequency: 70 -Wrong duration: 196 -Wrong route: 11
Shrestha R, 2019 (280)	The trained pharmacy personnel (1 assistant pharmacist and 1 pharmacist working in same hospital) collected data on the WHO prescribing indicators and PE (parameters were prepared by studying WHO practical manual on guide	NR	2 months	770 prescriptions, 2448 drugs	-PE: 1458	-Wrong dose/strength: 11 -Wrong/suboptimal drug: 4 -Wrong route: 5 -DDI: 249 -Others: 1189

	to good prescribing and previous studies) retrospectively					
ME: medication errors; PE: prescribing errors; NR: not reported; DDI: drug-drug interactions						

4.3.7 Prevalence based on the types of prescribing errors

Nineteen studies classified types of prescribing errors (Table 4.5), with wrong dose/strength (n=16) being reported by the most studies, followed by wrong/suboptimal drug (n=11), errors in relation to duration of use (n=7), and errors in relation to frequency of prescribed medications (n=7). Other types were wrong route, wrong/omitted patient directions, drug-drug interactions, contraindication, and others (e.g. duplicate therapy, inappropriate use of abbreviations).

A wide range of prevalence of dosing errors (overdose or underdose) was reported with errors ranging from 0-41% of all medications prescribed (Figure 4.4). Among studies (n=13) that reported the total number of patients, the rate of dosing errors per patient ranged from 0 to 2.76 (appendix 8, figure 3). In a retrospective study that had prescriptions as a denominator, 112 (25.5%) errors were detected in 479 prescriptions (279). Another study conducted in ambulatory care centers found 1099 dosing errors but no denominator was provided (267).

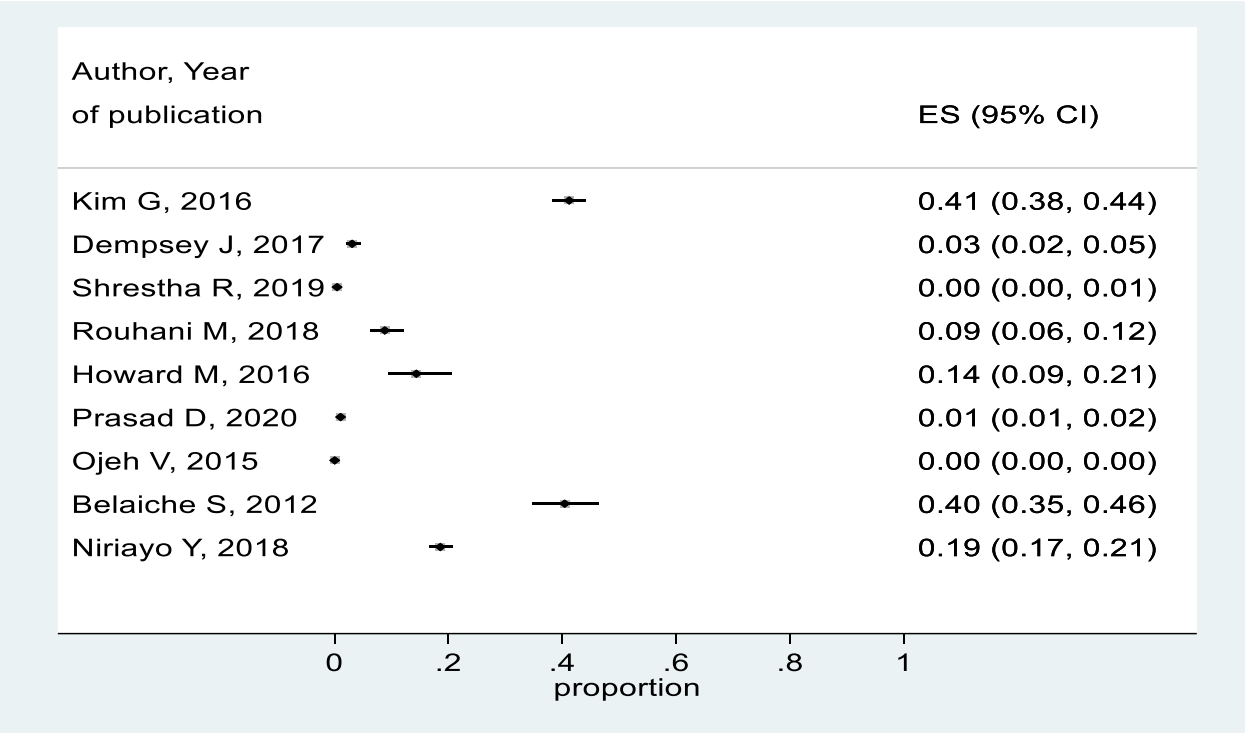

Figure 4. 4 Forest plot of medications with dosing errors as a proportion of total medications

The range of prevalence of wrong or suboptimal drug errors per prescribed medications was found to range between 0-19% of all medications prescribed (Figure 4.5), while nine studies found a range of dosing errors rates of 0.01 to 0.79 per patient (appendix 8, figure 4). Al-Khani et al (2013) reported 242 dosing errors but no denominator was reported in this study (267).

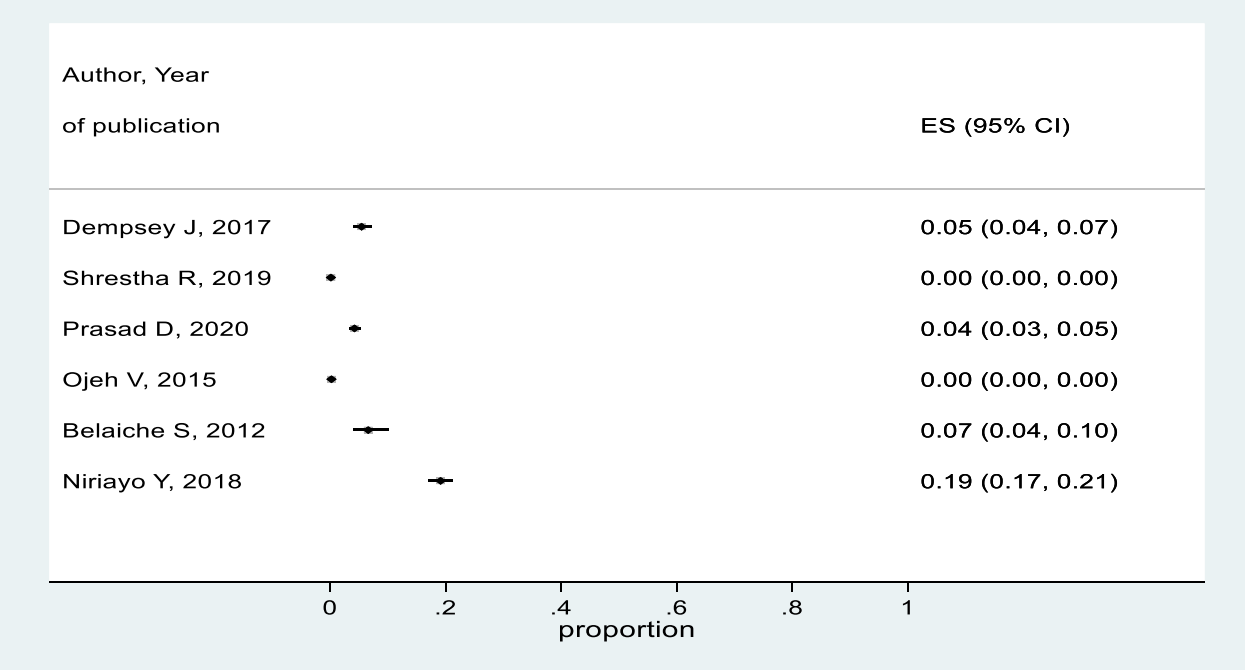

Figure 4. 5 Forest plot of medications with wrong/suboptimal drug errors as a proportion of total medications

Among studies assessing errors in relation to duration of use (n=7), only one study reported the total number of prescribed medications (n=1400), of which 14% (n=196) had an error (Figure 4.6) (265). Four studies reported the total number of patients, with the rate per patient with errors in relation to the duration of use ranging from 0.0 to 0.38 (appendix 8, figure 5). In a retrospective study that focused on NSAIDs-related errors, 44 duration of use errors were identified in 479 prescriptions (279). Around 2.4% of prescribing errors were found to be duration of use errors in another retrospective study that did not provide a denominator (267).

Seven studies reported errors in relation to the frequency of prescribed medications, of which only two prospective studies conducted in hospital-based outpatient departments provided the total number of medications. The prevalence per prescribed medications was 5% in the study with a 4-month follow-up duration (265), while it was 0.0% in another study that had 12-month follow-up duration (Figure 4.7) (264). In four studies that reported the total number of patients, the proportion of frequency errors per patient ranged from 0.01 to 0.08 (appendix 8, figure 6). In a study that reported the overall number of prescriptions and focused on NSAIDs, only nine (1.88%) frequency errors were detected in 479 prescriptions (279). Around 8.7% of prescribing errors were found to be frequency errors in a study that did not report a denominator (267).

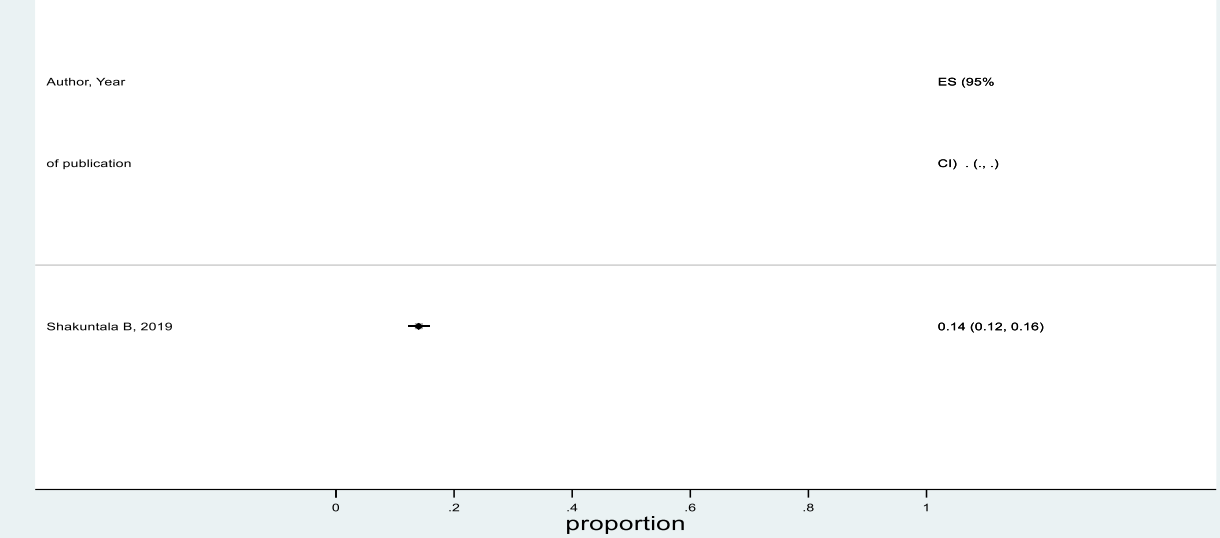

Figure 4. 6 Forest plot of medications with duration errors as a proportion of total medications

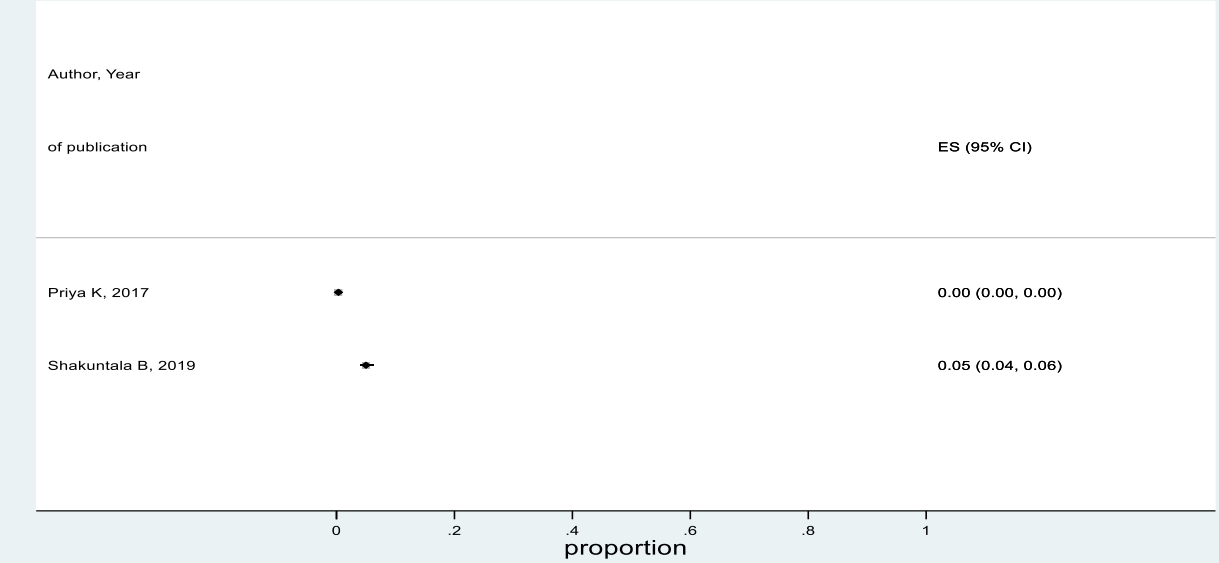

Figure 4. 7 Forest plot of medications with frequency errors as a proportion of total medications

4.3.8 Severity of medication errors

Out of the six articles that reported severity outcomes, four described the method used for categorization (Table 4.6). Various methods were used to classify severity which hindered identifying common patterns. The number of ranks (e.g. mild, moderate) in the used severity scales varied from two (263, 269) to seven ranks (273). Although most consequences of medication errors were mild to moderate and were not linked to patient harm, incidents leading to potentially lethal consequences were reported in one study (270).

Table 4. 6 Outcomes from studies reporting on severity of medication errors (n=6)

Author, year of publication	Methodology specific to severity classification	Number of errors for each severity class reported
Carollo J, 2017 (269)	NR	-Errors but no harm: 4862 -Error with harm: 5
Duarte et al, 2018 (270)	According to the methodology proposed by Overhage and Lukes	-Without error: 0 -Minor:91 -Significant: 140 -Serious: 114 -Potentially lethal: 1
Hernández S, 2018 (273)	Based on a scale of 0 to 6, where the higher the number the more severe the incident	-Potential error: 3 -No damage was caused to patient: 90 -Damage was caused and needed monitoring: 0 -Damage was caused accompanied by changes in vital signals and needed monitoring: 0 -Needed treatment with other medication and required hospitalization or a length of stay in a hospital: 0 -Permanent damage: 0 -Death: 0
Prasad D, 2020 (263)	NR	-Errors but no harm: 516 -Error with harm: 318
Priya K, 2017 (264)	According to the NCCMERP categorization	-(A-C)-ME doesn't cause any harm: 100 -(D)-ME required monitoring to confirm that it resulted no harm to the patient: 40 -(E-I)-harmful ME: 0

Shrestha R, 2019 (280)	-Reported for DDI only -Using drug interaction checker provide by Medscape	-Minor: 82 -Moderate (monitor closely): 156 -Serious: 11
NR: not reported; DDI: drug-drug interactions		

4.3.9 Contributory factors to medication errors

Of the 24 studies, 22 reported the contributory factors leading to medication errors (Table 4.7). None of these studies used theories/models/frameworks during data collection or analysis. The synthesis of contributory factors using Reason's model showed that 20 studies reported that latent conditions were a contributory factor to medication errors, while 15 studies reported active failures as a contributory factor.

Inadequate training or knowledge was a common latent condition reported by studies. Examples include poor training specific to special populations (particularly older patients with polypharmacy) and lack of knowledge related to updated therapeutic guidelines. Performance deficits were also common, largely due to duplicate therapy.

Among studies that reported active failures, eight highlighted mistakes, eight highlighted violations, six highlighted slips, and two highlighted lapses. Inappropriate use of abbreviations and incomplete prescriptions were example of violations. There was a considerable diversity among the contributory factors leading to mistakes. Examples include dosing errors due to failure to account for risk factors (e.g. elevated creatinine) and prescribing a medication that the patient is known to have an allergic reaction to it.

Table 4. 7 Outcomes of studies reporting on contributory factors to medication errors

Author, year of publication	Active failures and types	Latent conditions and types
Abramson E, 2011 (257)	-Mistake: prescribing errors -Violation: inappropriate use of abbreviations	-Lack of e-prescribing
Abramson E, 2013 (258)	-Mistake: wrong medication components -Violation: inappropriate use of abbreviations	-Performance deficit (wrong patient direction)
Al Khawaldeh T, 2017 (271)	NR	-Inadequate training/knowledge -Performance deficit (not checking prescription and stability, lack of double checking) -Heavy workload and lack of time -Shortage of staff -Lack of resources (protective equipment)
Al-Khani S, 2013 (267)	-Slips: look alike or sound alike, selecting the incorrect medication	-Performance deficit (duplicate therapy)
Assiri G, 2019 (268)	NR	-Inadequate training/knowledge (specially for specific population: elderly, polypharmacy, male)
Belaiche S, 2012 (272)	NR	-Inadequate training/knowledge (specially for specific population: multiple concomitant comorbidities and polypharmacy) -Fragmentation of care -Heavy workload and lack of time
Bell S, 2020 (259)	NR	-Misunderstanding and miscommunication
Bicket M, 2018 (260)	-Violation: inappropriate use of abbreviations, incomplete prescriptions	-Inadequate training/knowledge (physicians make less errors as compared to trainee and nurses) -Lack of e-prescribing
Carollo J, 2017 (269)	-Slips: dispensing errors (wrong medication) -Lapses: omission of medication components -Violation: inappropriate use of abbreviations	-Lack of documentation (duplicate dose administered) -Performance deficit -Lack of e-prescribing -Unstandardized prescription process
Dempsey J, 2017 (261)	-Mistake: prescribing errors	-Inadequate training/knowledge -Fragmentation of care
Duarte et al, 2018 (270)	-Mistake: prescribing errors -Slips: incorrect patient -Violation: incomplete prescriptions	NR

Hernández S, 2018 (273)	-Slip: dispensing errors	-Inadequate training/knowledge
Howard M, 2016 (262)	NR	-Inadequate training/knowledge (specially for specific population: female, elderly, altered kidney function)
Kim G, 2016 (274)	-Mistake: wrong dose	-Inadequate training/knowledge
Lee P, 2016 (275)	NR	-Inadequate training/knowledge (specially for immunosuppressant which have narrow therapeutic window) -Performance deficit (duplicate therapy)
Niriayo Y, 2018 (276)	NR	-Inadequate training/knowledge (specially for specific population: female, elderly, multiple concomitant comorbidities and polypharmacy, new guidelines and evidence) -Performance deficit (duplicate therapy) -Lack of patient involvement in decision making
Ojeh V, 2015 (277)	-Mistake: allergic reaction -Slips: incorrect patient	-Inadequate training/knowledge (specific to HIV due to the changes in guidelines and complex nature of HIV) -Performance deficit (duplicate therapy) -Unstandardized prescription process
Prasad D, 2020 (263)	-Slips: dispensing errors (wrong quantity) -Lapses: omission of diagnosis	-Inadequate training/knowledge (specially for specific population: female) -Heavy workload and lack of time -Interruption and distraction in the environment -Absence of quality assurance into academic education
Priya K, 2017 (264)	-Mistake: allergic reaction	NR
Rouhani M, 2018 (278)	-Violation: noncompliance to protocol (standard form)	-Inadequate training/knowledge (standard form and calculations)
Shaikh A, 2017 (279)	-Violation: inappropriate use of abbreviations, incomplete prescriptions	-Inadequate training/knowledge -Lack of e-prescribing
Shakuntala B, 2019 (265)	NR	NR
Shrestha R, 2019 (280)	-Mistake: prescribing errors -Violation: incomplete prescriptions, carelessness, prescribing by brand name	-Inadequate training/knowledge -Performance deficit -Lack of guidelines
Thakur H, 2013 (266)	NR	NR
NR: not reported		

4.3.10 Intervention to mitigate medication errors in outpatient and ambulatory settings

Only two types of interventions were identified from the seven studies that implemented interventions to minimize medication errors (Table 4.8). Pharmacist-delivered interventions (261, 264, 270, 272, 275, 277) were the most commonly evaluated (n=6), while only one study evaluated the effectiveness of electronic prescribing (e-prescribing) software (257). It is noteworthy that there was a lack of randomized controlled trials (RCT) and all studies had cross-sectional or observational design; hence they were of poor quality to evaluate interventions. Additionally, most studies lacked a comprehensive and sufficient description of the intervention characteristics and outcomes.

The study that implemented e-prescribing was the only one to report the number of medication errors before and after the intervention (257). The remainder reported the total number of interventions or preventable overall medication errors. The e-prescribing study analyzed 9385 prescriptions for 5955 patients and assessed that 19,571 out of 19,956 errors could have been prevented by implementing the basic and advanced versions of the clinical decision support (CDS) systems. All illegibility errors resolved after applying the basic version of the system (257). Among studies that did not report pre and post intervention outcomes, the number of interventions ranged from 64 in a study that included 60 patients (261) to 843 in a population of 1271 patients (275).

Among studies that proposed pharmacist-led interventions, three studies conducted direct consultation sessions with patients (272, 275, 277), two performed revisions of electronic records/prescriptions (264, 270), and one combined records checking with

medication reconciliation (261). Four out of the six studies also explored intervention subtypes (e.g. change to alternative medication, adjust dose) (261, 270, 272, 277); however only one reported the methodology used for this categorization (270). The most common types of interventions sub-classes were adjusting one or more regimen components (e.g. dose, duration), changing to alternative therapy, adding medication, and stopping unnecessary medication.

Table 4. 8 Outcomes from studies reporting on intervention outcomes (n=7)

Author, year of publication	Intervention characteristics	Post-intervention number of errors	Total number of interventions/ preventable errors	Methodology for intervention subclassification (if any)	Intervention subclassification (if any)	Acceptance rate
Abramson E, 2011 (257)	E-prescribing with either basic or advanced CDS. Each error was examined to determine whether using e-prescribing with either basic or advanced CDS could have prevented the error	-PE: 385 -Wrong dose/strength: 7 -Wrong frequency: 3 -Wrong duration: 0 -Wrong/omitted verbal patient direction: 5 -Others: 370	3058	Not applicable	Not applicable	Not applicable
Belaiche S, 2012 (272)	Pharmaceutical consultations by the pharmaceutical team (1 senior clinical pharmacist and 1 clinical pharmacy resident) to patients considered at high risk of presenting ME	NR	263	NR	-Adjustment of dose/frequency/duration: 111 -Change to alternative medication: 62 -Additional drug therapy required: 84 -Change to alternative medication: 12 -Medication without indication: 46 -Others: 10	NR
Dempsey J, 2017 (261)	Medication reconciliation completed by a pharmacist. An in-depth review of each patient's	NR	63	NR	-Change to alternative medication	NR

	medical record and medication profile was also performed				-Additional drug therapy required -Numbers not reported	
Duarte et al, 2018 (270)	The pharmacist evaluated prescriptions according to a set criteria such as using treatment protocol and dosage calculations	NR	346	The tool used is adopted from Cardinal and Fernandes	-Adjustment of dose/frequency/duration: 176 -Change to alternative medication: 62 -Additional drug therapy required: 14 -Others: 94	99.4%
Lee P, 2016 (275)	At each visit, the transplant pharmacist reviewed and optimized the medication regimens. Any errors were discussed with the physicians-in-charge, and they were either resolved or resulted in actions taken to address the specific errors	NR	843	NR	NR	-Accepted: 753 -Accepted with modification: 33 -Overall: 786 (93%)
Ojeh V, 2015 (277)	Eight clinical pharmacists trained in HIV pharmacotherapy with a work experience of 4-12 years provide pharmaceutical care services. At every fill/refill visit, pharmacists engaged in face-to-face interaction with the patient to verify the accuracy of prescription with	NR	420	NR	-Adjustment of dose/frequency/duration: 32 -Change to alternative medication: 67 -Additional drug therapy required: 87 -Medication without indication and offending agent: 77	93%

	consideration to clinical and laboratory parameters				-Others: 157	
Priya K, 2017 (264)	The pharmacist checked all medications for prescribing errors	NR	226	NR	NR	61.9%
CDS: clinical decision support; PE: prescribing errors; NR: not reported						

4.4 Discussion

4.4.1 Statement of key findings

The findings from this systematic review highlighted that medication errors were common (prevalence of 23-92% per prescribed drugs) in outpatient and ambulatory settings, while acknowledging variation in the ranges of prevalence estimates in individual studies. Prescribing errors were the most frequently studied type of errors, with a prevalence of 0-91% errors per all prescribed medications. The most common incident types were dosing errors (prevalence of 0-41% per prescribed drugs) and suboptimal/wrong drug errors (prevalence of 0-19% per prescribed drugs), followed by errors in relation to duration of use and frequency of prescribed medications. Mild to moderate consequences from medication errors were predominant; however incidents leading to significant harm and death were also reported. Notably, latent conditions, including inadequate training or knowledge, were more common than active failures. Among active failures, mistakes and violations were the most frequent contributory factors. Pharmacist-led interventions and e-prescribing software have been studied to reduce medication errors in these settings; however studies lacked randomized design and long-term follow-up.

4.4.2 Interpretation of findings

This review suggests that medication errors are common in outpatient and ambulatory settings. The range of prescribing errors rates from our findings was substantially higher than the rate of errors reported in a systematic review of 63 studies focusing on hospitalized patients (106). While it is expected that medical problems and interventions in outpatient and ambulatory settings are less complex than in inpatient setting, these

high numbers in the former settings necessitate attention from decision makers and other stakeholders to develop and implement prevention strategies.

In line with previous research conducted in various populations and settings, prescribing errors were the most frequently studied, with dosing errors constantly being the most prevalent (107, 176, 207). Whilst previous studies have reported active failures as the predominant contributory factors to medication errors (72, 189, 196, 207), latent conditions particularly the lack of knowledge and training were the most frequent in outpatient and ambulatory settings. The issue of supervisory and managerial inadequacies was also raised in studies that investigated the factors contributing to diagnostic errors in these settings (95, 99, 100).

Amongst active failures, mistakes and violations were the two most common contributory factors in outpatient and ambulatory settings. This finding is also distinct from what has been observed in other settings, in which slips, lapses, and mistakes were the three most common factors (72, 189, 196, 207). It is worth pointing out that most violation cases in this review were attributed to the inappropriate use of medical abbreviation.

It is noteworthy that method of identifying and validating medication errors were poorly reported across studies. This reinforces findings from previous research that described the process of identifying medication errors as fraught with inaccuracies and systematic bias (72, 281). Additionally, all studies had cross-sectional or observational design with the lack of dissemination and implementation design such as randomized controlled trials. Additionally, most studies lacked a comprehensive description of the intervention

characteristics and outcomes. Therefore, no conclusions could be drawn about the effectiveness of the proposed interventions.

There was a notable variation regarding the classes of medications associated with errors; however in line with previous systematic reviews, cardiovascular drugs were the most frequently reported therapeutic group (72, 253, 282). Some treatment modalities that are not usually seen in other settings have emerged in this review such as analgesics and vitamins (176, 253). These classes might seem simple as they mainly treat mild conditions. Nonetheless, some of them have many restrictions and could lead to serious adverse events such as NSAIDs and opioids (283).

4.4.3 Implications for practice and research

Medication errors (and its sub-classification) are common in outpatient and ambulatory settings even though there was variation in the data. This finding highlights the need to reduce medication errors in these settings. The comprehensive synthesis of contributory factors presented in this thesis facilitates the development of multifaceted theory-based interventions tailored to the identified factors. Theory-based interventions are expected to yield promising outcomes as other methods of developing interventions (i.e. pragmatic approach or ISLAGIATT [It Seemed Like A Good Idea At The Time] principle) were checkered, with some showing unfavorable outcomes or no benefit at all (50, 238-242).

Latent conditions were the main contributory factors identified in outpatient and ambulatory settings. Hence, it is believed that dedicating more efforts and allocating more resources by policy makers, healthcare managers, and other stakeholders towards these settings will have a positive impact. The review also emphasizes the insufficient

knowledge and training amongst healthcare professionals; therefore educational sessions that are based on structured needs assessment are expected to mitigate medication errors in these settings. Furthermore, prescribing errors were the most common type of medication errors in this review. Previous studies showed that pharmacist-led and technology-facilitated interventions lead to a reduction in prescribing errors and improvement in health outcomes (135, 284, 285); hence they could also be beneficial in these settings.

Future research should focus on the development of theory-based multifactorial interventions that incorporate healthcare managers, pharmacists, technologies, and education. The UK Medical Research Council (MRC) framework could be utilized to develop effective complex interventions (216). This framework incorporates theory to identify behavioral determinants to target in subsequent interventions and to ensure proper translation into practice (216). Moreover, studies with high quality design (i.e. randomized controlled trials) that aim to evaluate the long-term outcomes of interventions are needed to accurately measure the effectiveness of these interventions.

Poor reporting of the method of identifying and validating medication errors (e.g. instruments, personnel, training) was recognized across studies. It is strongly encouraged that future researchers adopt a well- established and validated methodology to identify and classify medication errors and to train individuals involved in the process. It also is recommended to address issues related to validation of identified errors, which could be done through multiple methods such as double checking and calculating interrater reliability.

None of the included studies followed a structured approach to identify and classify contributory factors. Adopting a theory-based methodology such as Reason's Accident Causation Model will ensure that the identified contributory factors are inclusive and hence reduce the risk of reporting bias. It also will increase our understanding of these factors which will facilitate the process of translating them into effective interventions.

4.4.4 Heterogeneity

Although meta-analysis was planned; it was not conducted due to the substantial between-studies heterogeneity. This was expected due to multiple factors including the variation in the service specialty which also affects the acuity of the patients and the number of medications per patient. For instance, some studies focused on high-risk patients or pharmacological classes such as chemotherapy or nephrology patients (271, 272), while others were conducted in family medicine clinics where patient cases are usually milder (268). Additionally, the main aim of the studies was not always to quantify errors, this influenced the level of detail in reporting this outcome.

The length of follow-up varied significantly across studies from 15 days to 4 years which could also contribute to the high heterogeneity (260, 273). Moreover, various definitions of medication errors and its sub-classifications were adopted in the included studies. For example, it was evident that the rates of medication errors were higher in studies that counted illegible prescriptions as medication errors.

Another factor that may have influenced the heterogeneity is the various methodology adopted to detect medication errors. The robustness of the identification method could largely impact the number of identified errors. Well-designed studies that follow a

standardized and structured methodology is expected to show a more reliable count of errors. Other factors that may have affected the heterogeneity is the study design as well as staffing levels and their expertise in the centers where studies were undertaken.

4.4.5 Strengths and limitations

The main strength of this systematic review is its novelty in being the first attempt at collating and synthesizing data from all studies exploring medication errors in outpatient and ambulatory settings. A theoretical approach to classifying contributory factors was adopted, which enhances the reliability and validity of our outcomes and facilitate the development of interventions. Moreover, the included studies were from different countries which could increase the generalizability of the findings.

This review was limited by the moderate overall quality of included studies which could undermine the quality of the findings from this review. Additionally, the search strategy was limited to articles published in English language. Due to substantial clinical and methodological heterogeneity pooling of outcomes was judged inappropriate and hence meta-analysis was not performed. The synthesis of contributory factors was subjected to reporting bias as it relies on what has been reported by the original studies. It is also worth noting that classifying contributory factors according to Reason's model could be subject to interpretation bias, particularly when the error circumstances and conditions were not thoroughly discussed. Additionally, evidence suggests that medication errors are underreported (170, 286) due to multiple causes such as fear, lack of effective error reporting system, lack of peer and managerial support to practitioners who committed an error, and work overload (35, 72, 287). Hence, included studies that used incident

reporting systems to quantify medication errors are likely to underestimate the true prevalence causing downward bias in the error rates in the current review.

4.5 Conclusion

This systematic review suggests that medication errors in outpatient and ambulatory settings are highly prevalent; however wide variation in the prevalence range was observed across studies. The factors contributing to medication errors were mainly latent conditions, including inadequate training or knowledge of healthcare practitioners in relation to special populations and updated therapeutic approaches. There is a need for the development of theory-based multifactorial interventions to minimize medication errors in outpatient and ambulatory settings. These interventions should include organizational and system-level strategies (e.g. effective resource allocation), multidisciplinary collaborations, effective integration of pharmacists, health information technology, as well as educational and training programs. Randomized controlled trials are needed to develop and evaluate the long-term outcomes of complex interventions in these settings.

Chapter 5: Discussion and conclusion

This chapter will provide an overview of the overall thesis aim, main findings, as well as a discussion of the methodology adopted in this thesis. It also will attempt to triangulate findings from the umbrella review and systematic review presented in chapters three and four respectively. Finally, the implication of the findings from this thesis on practice and research will be presented.

5.1 The overall aim of the thesis

The primary aim of this body of work was a) to systematically evaluate contributory factors to medication errors in healthcare settings in terms of the nature of these factors; methodologies and theories used to classify them; and terminologies and definitions used to describe them, b) to synthesize the literature on the prevalence, nature, contributory factors, and interventions to minimize medication errors in outpatient and ambulatory settings.

To achieve the first aim of this thesis, an umbrella review of published systematic reviews that investigated factors contributing to medication errors in all healthcare settings was conducted. For the second aim, a systematic review of studies exploring medication errors in outpatient and ambulatory settings was undertaken.

5.2 Summary of findings

In phase one of this thesis, a comprehensive summary of contributory factors to medication errors across diverse healthcare settings was presented. It was evident that

decision-making mistakes, which include failure to consider risk factors (e.g. chronic kidney disease and pediatrics), were the most commonly reported contributory factor. This was followed by factors related to the organization and environment, including lack of knowledge, insufficient training, work overload, inadequate staffing levels, illegible prescriptions, distraction and interruptions, and poor communication. Amongst the few reviews that followed a structured method to classify contributory factors, the use of theory and Reason's model was common. A range of terminologies and definitions were used to refer to contributory factors. Multiple interventions were proposed in the included reviews to mitigate the contributory factors and subsequently reduce errors; however, none of the reviews evaluated the effectiveness of the suggested interventions.

Finding from the umbrella review highlighted multiple methodological deficiencies in the included systematic reviews, mainly the lack of prespecified methodology to identify and classify contributory factors. Despite the value and benefit of theoretical basis in undertaking exploratory and interventional research to identify and target different behaviors, there was a lack of the use of theoretical frameworks across included studies. The umbrella review also demonstrated the lack of systematic reviews that explored medication errors in outpatient and ambulatory settings. The subsequent phase of this thesis hence aimed to systematically synthesize the evidence from studies conducted in these settings.

Findings from the systematic review showed that medication errors are common in outpatient and ambulatory settings even though there was a notable variation in the ranges. In line with studies conducted in other settings and populations, most errors were

prescribing errors and dosing errors (107, 176, 207). Other common incident types were suboptimal/wrong drug errors, errors in relation to duration of use, and frequency of prescribed medications. Whilst mild to moderate consequences from medication errors were most common; incidents leading to severe harm were observed including errors leading to significant harm and death.

The recommendations generated based on the findings from the umbrella review (such as the use of theory) were applied to the synthesis of contributory factors in the systematic review. This allowed this thesis to highlight a contributory factor that has been poorly reported in the published literature, mainly the system failures. Whilst these factors have been reported in other settings (72, 207), they were recognized to be the key contributory factors to medication errors for the first time in outpatient and ambulatory settings. Amongst active failures, mistakes and violations were the most frequent contributory factors.

Interventions to minimize medication errors in outpatient and ambulatory settings were only discussed in seven studies. Pharmacist-led interventions and e-prescribing software were the only types of interventions that emerged from included studies. The intervention research in these settings was limited in terms of quantity, of poor quality, and the lack of long-term follow-up.

5.3 Discussion of methodology adopted in the thesis

The reporting of both phases of the current thesis was in accordance with well-developed reporting guidelines to ensure the inclusion of all necessary components and

subsequently guarantee the trustworthiness and the reproducibility of the outcomes. For the umbrella review, the Joanna Briggs Institute (JBI) reporting methodology was adopted (123). We also referred to the Preferred Reporting Items for Overviews of Reviews (PRIOR) tool for areas that were not covered by the JBI manual (143, 162). For the systematic review, the recommendations provided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline were followed (133).

The protocols for both reviews were registered and published prospectively with PROSPERO, the international prospective register of systematic reviews. This ensures the transparency and reproducibility of the methods and reduces the potential for bias in conduct and reporting (288). To ensure retrieval of all relevant literature, both current reviews conducted a comprehensive search of multiple databases and search engines followed by screening the reference lists of the included studies. However, the search strategy was limited by the inclusion of English publications only. All screening stages were undertaken through a conventional double-screening approach. This enables avoiding both systematic and random errors as it ensures the standardized application of the eligibility criteria and enhance the ability to identify and rectify any errors in the process (289).

The data extraction sheet for the umbrella review was adapted from the JBI Reviewers' Manual with modifications to serve the purpose of the current review. This approach ensures the inclusion of all relevant components that should be presented in an umbrella review. For the systematic review, a data extraction sheet was developed through discussions and iterative feedback with the supervisory team. The instruments were also piloted to ensure that they are comprehensive and to resolve any confusion.

One of the main limitations in both reviews was the single data extraction and quality assessment. A randomized controlled trial showed that single data extraction was associated with more errors as compared to double data extraction (290). Therefore, although double data extraction and critical appraisal is resource intensive, it has been advocated by multiple health institutes such as the Agency for Healthcare Research and Quality (AHRQ), the Center for Reviews and Dissemination (CRD), and the Institute of Medicine (IOM) (289). To attempt to reduce the impact of the single data extraction and quality assessment, a pilot phase of dual extraction and appraising was conducted on a small percentage of the records in order to resolve any confusion. A single extraction was undertaken for the remainder of the studies with one of the supervisors checking all extracted data. Although a pilot phase may reduce error due to ambiguous or misapprehended data extraction or quality assessment tools, it is unlikely that it will prevent all types of errors particularly random error (291).

Iterative feedback within the team members was provided throughout the development of the protocols, undertaking of the reviews, and synthesis of findings. Additionally, the umbrella review was published under the title “An umbrella review of systematic reviews on contributory factors to medication errors in healthcare settings” and the constructive comments and suggestions received from the peer revision have been incorporated into the current thesis. Moreover, statistical analyses were supported by an expert statistician which enhances the reliability and robustness of the quantitative findings.

To ensure that the systematic review presented in chapter four of this thesis avoids the common methodological pitfalls of published reviews on contributory factors to medication

errors, learning from the umbrella review was applied to the conduct of the second phase of the thesis. Therefore, Reason's Accident Causation Model was utilized as a theoretical basis for the synthesis of factors contributing to medication errors. Relevant definitions were also provided in the methods section and consistent use of terminologies was maintained throughout this research thesis.

The use of theory in exploratory and interventional research has been strongly recommended to identify and target different behaviors (64, 216). In the second phase of this thesis, a theoretical framework was utilized to identify and classify contributory factors. This enhances the reliability and validity of the findings and facilitate the development of potentially effective interventions tailored to the identified factors. Nevertheless, the use of Reason's model subjects the synthesis to interpretation bias, particularly when the error circumstances and conditions are not thoroughly presented.

To ensure the rigor of the research and the trustworthiness of the outcomes, validated frameworks for quality assessment were employed. The main challenge that was faced while planning the umbrella review was the scarcity of quality assessment tools that sets minimum requirements to assure the quality of such reviews. To overcome this issue, a scoping search of previously published umbrella reviews was undertaken to identify all areas that have been previously reported; and incorporate them in the current review.

Additionally, the authors evaluated the current umbrella review according to the assessment of multiple systematic reviews 2 (AMSTAR 2) tool to ensure its reliability and quality (154). The research team recognizes that this tool is only validated for systematic reviews; however, given the similarity in design and methodology, it can be safely

assumed that it is reasonable to utilize the AMSTAR 2 tool until a tool that is specific for umbrella reviews is available. The current umbrella review met all the requirements of the tool. The assessment of the umbrella review according to the AMSTAR 2 tool is presented in appendix 9, table 1.

For the systematic review, the methods adopted were also evaluated against the minimum requirements provided by the AMSTAR 2 tool to ascertain reliability and quality of the review (154). The current systematic review met all the criteria for the 16 components of the instrument (appendix 9, table 2).

5.4 Implication for practice and research

The comprehensive synthesis of the factors contributing to medication errors across healthcare settings presented in this thesis enables the development of holistic theory-informed interventions tailored to these factors. Decision-making mistakes (i.e. error of judgment) and organizational factors were the most identified contributory factor. Therefore, multifaceted theory-based interventions that targets factors from the organizational level down to specific tasks at the individual level are needed.

The high prevalence of medication errors highlighted in the of body of this work shed light on the substantial burden of medication errors in outpatient and ambulatory settings. Furthermore, findings from this thesis increase the understanding of the nature and contributory factors specific to these settings. Unlike the findings from the umbrella review, latent conditions were the most common in outpatient and ambulatory settings followed by decision-making mistakes. This provides directions for policy makers and

future researchers in designing theory-based interventions to reduce medication errors and improve patient safety in these settings.

This thesis emphasizes the need for multifactorial interventions in different healthcare settings. These interventions should incorporate organizational and system-level strategies (e.g. effective resource allocation), interdisciplinary collaborations, effective integration of pharmacists, maximizing the benefit from health information systems, and educational and training programs. As latent conditions were the most common in outpatient and ambulatory settings, there is a particular need for improving managerial decision-making process and introducing structural-level policy changes in these settings. Although the role of pharmacists and technology has expanded in recent years (228-230), several reports suggests that they remain underutilized (231-234). Hence, developing benefits maximization strategies is of extreme importance to harness the full potential of such interventions.

It is pivotal that policy makers prioritize and concentrate efforts on the development of innovative theory-based mitigation strategies. Developing interventions using theoretical frameworks provides an in-depth understanding of the structural and psychological determinants of behavior at different levels (i.e. individual, interpersonal, organizational, community, and societal levels). This enables theoretically informed interventions to create a sustainable behavior change (292). The use of theory to develop interventions and the long-term impact of such interventions will be for further exploration in the doctorate studies.

Research questions that could be addressed in future research are stated below with suggested study designs.

1- *What is the impact of multifaceted theory-informed interventions to reduce medication errors on the clinical, humanistic, and economic patients' outcomes in the outpatient and ambulatory settings?*

Multifaceted theory-informed interventions (including educational, technology, pharmacist-led, multidisciplinary teamwork, and organizational and system-level strategies) need to be developed to mitigate medication errors and subsequently achieve the ultimate goal of healthcare systems which is to foster a culture of patient safety and optimize care provided to patients. Therefore, it is pivotal to investigate the effectiveness of such interventions on clinically important outcomes to ensure that the overall purpose of the healthcare system is being served.

Limited previous literature showed that such interventions were effective in reducing medication errors and improving patient outcomes in other settings and patient cohorts (32, 134, 135, 173-175). Integrated interventions combining educational, technology, pharmacist-led, multidisciplinary teamwork, and organizational and system-level strategies are suggested to enhance the effectiveness and hence future efforts should be dedicated to developing theory-based complex interventions using the UK Medical Research Council (MRC) framework (216). Obtaining the best form of evidence requires the adoption of randomized controlled trial of integrated interventions against usual practice. Randomized controlled trials are known to deliver best forms of evidence as per the evidence hierarchy (293).

When implementing innovative interventions, it should be kept in mind that, although they might effectively reduce traditional human errors, several reports showed that their implementation could introduce new unknown types of errors, particularly when technology is involved (57). This could be attributed to the several interactions and interrelationships occurring in a nonfamiliar or unexpected manner between the interrelated components of the system (human, technology, organization, and social aspects) (51). Hence, it is also important to use suitable theories in order to understand the different interactions occurring between the system components. This will enable practitioners and decision makers to overcome the identified issues and subsequently maximize the benefit related to multifaceted interventions.

2- *What are the barriers and facilitators to implementation of innovative interventions to reduce medication errors in outpatient and ambulatory settings?*

To facilitate the process of implementing an intervention, it is imperative to understand the barriers and facilitators in order to ensure the effective use of the facilitators while trying to resolve or overcome the barriers. In recent years, there has been an in increasing interest in process evaluations alongside outcome evaluations of complex healthcare interventions (294). Process evaluations emphasize the relations between implementation, mechanisms of impact, and context (295). They may thus improve understanding of complex interventions, avoid biases in interpretation of outcomes, and enhance the fidelity and quality of implementation into practice (295, 296).

A suggested study design is a qualitative exploration such as interviews or focus groups. Mixed-method approach (exploratory sequential design) could also be useful by

conducting a cross-sectional survey after the qualitative study to generate typology (overarching taxonomy) of the identified barriers and facilitators.

Consolidated Framework for Implementation Research (CFIR) is an effective implementation conceptual framework that could be used to develop the survey tool. The framework allows the systematic assessment of the multilevel contextual factors (intervention, inner and outer setting, individuals, and implementation process) and enable the formulation of comprehensive taxonomies (297, 298). Specifying and aggregating the implementation determinants enables a holistic scene understanding and subsequently behavior change interventions could be designed.

3- How can roles of pharmacists be expanded in outpatient and ambulatory settings?

As drug therapy experts, pharmacists are uniquely positioned to provide drug therapy management services in collaboration with patients, physicians, and other members of the healthcare team. In published literature that focused on settings other than the outpatient and ambulatory settings, several pharmacist-delivered interventions have shown positive impact on reducing medication errors and improving patient outcomes. These interventions include one or a combination of the following including implementing unit-based pharmacist, reviewing/verifying medication orders, delivering educational sessions to healthcare providers, attending rounds, medication therapy management, and medication reconciliation (32, 134, 135, 299-302). Innovative interventions have also been described in the literature such as telemedicine (or telepharmacy) services and pharmacist prescribing (303-305).

In recent years, pharmacists are increasingly being recruited in outpatient and ambulatory settings (306). This is attributed to the presumption that patients in these settings are likely to benefit from clinical pharmacist services (303). Although the impact of pharmacist-led interventions on medication errors in these settings is not yet clear, such interventions were associated with favorable outcomes related to disease management, patient self-management, and enhancing adherence (303).

4- *How can patient safety be improved, in particular to minimizing medication errors, in the context of non-medical prescribing (NMP)?*

Non-medical prescribing (NMP) such as independent pharmacist or nurse prescribing has been increasingly implemented in multiple countries to enhance access to medicine and streamline patient care (307). For NMP to become widely accepted and used, decision makers, healthcare quality and safety bodies, and the public require evidence of the overall quality and safety of NMP. Therefore, it is important to ensure that NMP does not lead to an increase in medication errors and that it has the potential to introduce services that could enhance the quality and safety of patient care, while simultaneously minimizing costs.

Anecdotal evidence from case studies and clinical audits suggested that NMP is safe and can provide beneficial clinical and humanistic outcomes (308-310). Additionally, a Cochrane review published in 2016 compared resource utilization between NMP and medical prescribing showed that NMP was non-inferior to medical prescribing in relation to clinical and patient reported outcomes (311). A systematic review that included three

randomized controlled trials also demonstrated similar beneficial outcomes; however the evidence was of poor quality (312).

Although there is preliminary evidence of the value of NMP, high-quality research that conduct a robust evaluation of the safety and quality of NMP in comparison to medical prescribing is still needed. There also should be an evaluation of the impact of NMP across multiple clinical specialties and healthcare settings. Moreover, a systematic assessment of any potential increase in medication errors or introduction of new types of errors as a result of implementing NMP should be investigated thoroughly.

5- *Would the use of non-linear complex models provide a more useful and effective assessment of contributory factors to medication errors?*

Theory-based methodology is of value particularly in exploratory and interventional research. There is a plethora of theoretical frameworks that are available for scholars to choose from and utilize in their research (298). It is important to understand the pros and cons of each framework to determine its suitability for the intended study aim and design. This also applies to the theories used in the accident causation field.

Reason's Accident Causation Model could be criticized for being a linear complex model (63). Thus, it could be argued that it may be insufficient to completely embody the interconnected networks and the multidirectional interactions taking place in the complex healthcare system (66). Therefore, it is recommended to attempt to utilize a non-linear complex model [such as Systems-Theoretic Accident Model and Process (STAMP) or Functional Resonance Accident Model (FRAM)] to replicate the current systematic review

using the same design. By doing this, the findings from both reviews could be compared and inferences about whether the non-linear complex frameworks are more appropriate could be drawn.

6- *How can the methods of identifying and quantifying medication errors be optimized?*

Findings from the current systematic review, showed that the methods for identifying and validating medication errors were poorly reported across studies. Additionally, data collection process relied largely on analysis of medical record, observation, or reviewing incident reports. Previous research suggested that the available methods for measuring and quantifying medication errors, including the ones reported in the systematic review, have inaccuracies and systematic bias (72, 281). For instance, studies that utilized incident reporting systems to quantify errors are likely to provide underestimation because self-reporting of errors is rare (170, 286).

Some methods have previously been proposed in the literature to overcome the limitations reported in the currently available methods. This included the rapid discontinuations (i.e. abrupt stop) of medication orders as an expedient proxy for prescribing errors (43, 281). However, these methods have not received systematic analysis with modern technological advances. Therefore, future research should focus on the development of a systematic, valid, and efficient method to identify and quantify errors that address flaws in current methodology.

5.5 Conclusion

The body of work presented in this thesis has comprehensively synthesized the evidence on the prevalence, nature, and contributory factors of medication errors in outpatient and ambulatory settings. Recommendations provided in the first phase of this thesis were utilized for critical revision and synthesis of findings in the second phase.

The umbrella review presented in this thesis aimed to systematically evaluate the evidence on factors contributing to medication errors in terms of terminologies, definitions, classifications, methodologies, theories used, and contributory factors. Findings from this phase showed that decision-making mistakes due to failure to consider risk factors were the most common contributory factor, followed by factors related to the organization and environment such as understaffing and distractions. Inconsistency in terminology, definitions, and classification was observed in the included reviews. Additionally, most reviews lacked a prespecified methodology to identify and classify contributory factors. Moreover, none of the reviews evaluated the effectiveness of interventions in reducing medication errors. The comprehensive synthesis of contributory factors presented in this part of the thesis could possibly inform the development of holistic theory-based interventions that target different levels of the healthcare system. It also provides a comprehensive and evidence-based guidance for future researchers who intend to conduct high-quality research to explore factors contributing to medication errors.

The systematic review aimed to explore medication errors in outpatient and ambulatory settings in terms of prevalence, types, severity, contributory factors, as well as proposed interventions to reduce their occurrence. Finding from this phase showed that medication

errors, particularly prescribing errors, are prevalent in outpatient and ambulatory settings with a wide variation in the ranges noted across included studies. Dosing errors were the most common incident type, followed by suboptimal/wrong drug, duration, and frequency errors. The dominant contributory factors related to system and top-level management decisions. Findings from the systematic review highlights the need for multifactorial theory-based interventions that incorporate pharmacists, technology, and education. It is important to engage patients, clinicians, and wider stakeholders in the development, implementation, and evaluation of future interventions to ensure the acceptability and feasibility of these interventions to the end users.

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Appendices

Appendix 1: PROSPERO registration protocol for phase one (umbrella review)

Citation

Lina Naseralallah, Vibhu Paudyal, Derek Stewart, Malcolm Price. Synthesizing and critically appraising the evidence on factors contributing to medication errors: umbrella review. PROSPERO 2022 CRD42022321425Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022321425

Review question

Aim:

To systematically evaluate methodologies and theories used to synthesize factors contributing to medicationerrors in healthcare settings in existing systematic reviews

Objectives:

To assess the methodological rigor of systematic reviews investigating contributory factors related to medication errors in healthcare settings

To systematically evaluate and synthesize the methodologies, theories, models, frameworks, definitions, and terms adopted by systematic reviews to describe and classify contributory factors to medication errors

To systematically overview the adopted definition of medication errors and the terms used to describe medication errors

To evaluate how interventions aimed to prevent and mitigate medication errors, by addressing the identified contributory factors, have been classified in existing systematic reviews

To summarize and compare existing systematic reviews to identify overlap between published systematic reviews and identify gaps in literature

Searches

Databases: MEDLINE, CINAHL, EMBASE, Google Scholar (20 pages)

Terms: (medication error OR ((medication* OR transcrib* OR prescrib* OR dispens* OR administ*) AND(incident* OR mistake* OR error*))) AND (Systematic review* OR Meta-analysis).tw.

Limits: Systematic reviews, Meta-analysis, English (as applicable to the database), Human (as applicable tothe database)

Types of study to be included

Only systematic review with or without meta-analysis reporting on contributory factors regardless of themethodology adapted to identify these factors.

Narrative review, scoping reviews, and any other type of review will be excluded.

Condition or domain being studied

Contributory factors to medication errors occurring at any setting and relevant to any condition or pharmacological class of drugs. Interventional systematic reviews can be included as long as they report onfactors contributing to medication errors

For the purpose of this study, we will adopt the National Coordinating Council for Medication Error Reportingand Prevention (NCCMERP) definition of medication errors “any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer”. We will also capture the definitions of medication errors used by individual systematic reviews.

Participants/population

No restriction of the age, gender, or clinical specialty will be applied. This study is an umbrella review, thusonly systematic reviews will be included.

Intervention(s), exposure(s)

Medication errors. We are not assessing a particular intervention and its impact on medication error; thus thepresence of a certain intervention/exposure is not a requirement for studies to be included in this systematic review

Comparator(s)/control

None.

Main outcome(s) [1 change]

Qualitative outcomes related to the following:

Methodological rigor of systematic reviews investigating contributory factors related to medication errors inhealthcare settings

Methodologies, theories, models, frameworks, definitions, terms, and classes adopted by systematic reviews to describe and classify contributory factors to medication errors

The adopted definition of medication errors and the terms used to describe medication errors

The interventions aimed to prevent and mitigate medication errors, by addressing the identified contributory factors, have been classified in existing systematic reviews.

Additional outcome(s)

None.

Data extraction (selection and coding) [2 changes]

Two authors will independently screen the titles, abstracts, and full texts for eligibility. Discrepancies will beresolved by discussion with other team members.

A data extraction tool will be created (by discussion between authors to capture the objectives and byutilizing the PRIOR and JBI data extraction form) to abstract:

characteristics of the systematic review (study authors, year, study design, settings, number of studies and participants)

search details (databases searched, search timeframe)

population characteristics (age, sex, ethnicity, and stage of disease, as applicable)

assessments for publication bias (e.g. funnel plot, statistical test) and missing primary studies, analyses, or results (e.g., ROB-ME)

- If systematic review authors did not assess for publication or reporting biases, this should be noted withrationale if provided

methodological rigor of included systematic review (utilizing JBI tool)

methodologies, theories, models, frameworks, definitions, and terms to describe and classify contributory factors

definition of medication errors (or sub-classification) and terms used to describe medication errors

classification of interventions developed to address these factors (if any)

overlaps and gaps in current body of literature

Risk of bias (quality) assessment

Two raters will independently conduct the risk of bias assessment utilizing the Joanna Briggs Institute (JBI)10-item checklist for critical appraisal. Consensus will be sought through discussion with other team members.

Strategy for data synthesis [1 change]

For reported contributory factors, methodology of identifying and classifying contributory factors, definition and terms used to describe contributory factors and medication errors, and interventions developed to address contributory factors, a narrative approach to data synthesis will be employed, which will also includestudy characteristics tables to summarize relevant data according to the data extraction tool.

No quantitative synthesis will be carried out.

To assess the value of methods of included systematic review:

We will assess publication bias (e.g. funnel plot, statistical test) and missing primary studies, analyses, or results (e.g., ROB-ME) as reported by authors. If systematic review authors did not assess for publication orreporting biases, we will note this with rationale if provided

Risk of bias assessment utilizing the Joanna Briggs Institute (JBI) 10-item checklist for critical appraisal We will attempt at assessing the value of methodology utilized to assess contributory factors by assessing:

rationale provided by authors for employing a particular theory/framework

the ability of the employed method in identifying contributory factors

the effectiveness of the intervention developed to address the identified contributory factors (was the developed intervention successful in reducing medication errors or not)

The findings from our study will provide directions for future research in choosing a suitable methodology toidentify contributory factors according to the medication error types, setting, and population. Followed by further work, our results will assist the development of a proposed conceptual framework model to guide future interventions to mitigate medication errors. It will also identify gaps in literature (settings, population, medication errors types that have not been investigated yet for contributory factors to medication errors), which should be the focus of future research in order to design tailored interventions

Analysis of subgroups or subsets

None.

Contact details for further information

Lina Naseralallah

lxn107@student.bham.ac.uk

Organisational affiliation of the review

School of Pharmacy, College of Medical and Dental Sciences, University of Birmingham, Birmingham, UK

Review team members and their organisational affiliations

Ms Lina Naseralallah. School of Pharmacy, College of Medical and Dental Sciences, University ofBirmingham, Birmingham, UK

Dr Vibhu Paudyal. School of Pharmacy, College of Medical and Dental Sciences, University of Birmingham,Birmingham, UK

Professor Derek Stewart. College of Pharmacy, Qatar University, Doha, Qatar

Dr Malcolm Price. Applied Health Research, University of Birmingham, Birmingham, UK

Type and method of review

Intervention, Review of reviews, Synthesis of qualitative studies, Systematic review

Anticipated or actual start date

28 March 2022

Anticipated completion date

30 June 2022

Funding sources/sponsors

None.

Language

English

Country

England

Stage of review

Review Ongoing

Subject index terms status

Subject indexing assigned by CRD

Subject index terms

Humans; Medication Errors; Surveys and Questionnaires

Date of registration in PROSPERO

11 April 2022

Date of first submission

04 April 2022

Stage of review at time of this submission

The review has not started

Stage	Started	Completed
Preliminary searches	No	No
Piloting of the study selection process	No	No
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

Revision note

We decided to provide a synthesis of all contributory factors to medication errors reported in the literature. We believe that assessing overlap is not suitable for the purpose of this review. We are assessing the methodological quality of all reviews that looked into contributory factors to medicationerrors, therefore we believe that all reviews should be included regardless of their focus.

Appendix 2: Full search strategy for phase one (umbrella review)

1- Databases:

- Medline
- CINAHL
- EMBASE

Other search engines:

- Google Scholar (20 pages)

2- Search terms:

Medication errors:

- medication error [MeSH]
- OR ((medication* OR transcrib* OR prescrib* OR dispens* OR administ*) adj3 (incident* OR mistake* OR error*)) AND
- Systematic review* OR Meta-analysis – tw: search only in title and abstract

Limits:

- Systematic reviews
- Meta-analysis
- English (as applicable to the database)
- Human (as applicable to the database)

3- Search from Medline: Date: Tuesday, March 29, 2022

Filter: Systematic review, meta-analysis, English, Human

# ▲	Searches	Results
1	medication error.mp. or Medication Error/	14255
2	((medication* or transcrib* or prescrib* or dispens* or administ*) adj3 (incident* or mistake* or error*)).tw.	7830
3	1 or 2	16804
4	(Systematic review* or Meta-analysis).tw.	274496
5	3 and 4	375
6	limit 5 to (english language and humans and (meta analysis or "systematic review"))	294

4- Search from Embase: Date: Tuesday, March 29, 2022

Filter: Systematic review, meta-analysis, English, Human -Exclude Medline records

# ▲	Searches	Results
1	medication error.mp. or Medication Error/	20049
2	((medication* or transcrib* or prescrib* or dispens* or administ*) adj3 (incident* or mistake* or error*)).tw.	15455
3	1 or 2	26072
4	(Systematic review* or Meta-analysis).tw.	421343
5	3 and 4	613
6	limit 5 to (english language and humans and (meta analysis or "systematic review"))	432

3- Search from CINAHL: Date: Tuesday, March 29, 2022

Filter: Systematic review, meta-analysis, English

- All MeSH terms were similar to Medline

Search ID#	Search Terms	Search Options	Actions
S7	S3 AND S4	**Limiters** - Publication Type: Meta Analysis, Systematic Review **Expanders** - Apply equivalent subjects **Search modes** - Boolean/Phrase	View Results (515)
S6	S3 AND S4	**Expanders** - Apply equivalent subjects **Narrow by Language:** - english **Search modes** - Boolean/Phrase	View Results (821)
S5	S3 AND S4	**Expanders** - Apply equivalent subjects **Search modes** - Boolean/Phrase	View Results (830)
S4	TI (Systematic review* OR Meta-analysis) OR AB (Systematic review* OR Meta-analysis)	**Expanders** - Apply equivalent subjects **Search modes** - Boolean/Phrase	View Results (167,315)
S3	S1 OR S2	**Expanders** - Apply equivalent subjects **Search modes** - Boolean/Phrase	View Results (36,915)
S2	((medication* OR transcrib* OR prescrib* OR dispens* OR administ*) AND (incident* OR mistake* OR error*))	**Expanders** - Apply equivalent subjects **Search modes** - Boolean/Phrase	View Results (36,915)
S1	(MH "Medication Errors")	**Expanders** - Apply equivalent subjects **Search modes** - Boolean/Phrase	View Results (14,631)

Appendix 3: Data extraction sheets for phase one (umbrella review)

Characteristics of included systematic reviews							
Study ID	Author, year	Study design	Context (e.g. pharm class, settings, geographical region)	Aim	Total number of primary studies	Inclusion criteria	Exclusion criteria

Search details						
Study ID	Number of databases	Databases searched	Other sources (e.g. grey lit)	Search timeframe	Search limits	Specific terms for contributory factors

Assessments of overall quality of primary studies (as reported)							
Study ID	Tools utilized to assess methodological quality	Overall methodological quality	Tools utilized to assess quality of evidence	Overall quality of evidence	Publication bias (e.g. funnel plot, statistical test)	Other quality assessment (e.g. ROB-ME)	If not reported: rationale

Contributory factors						
Study ID	How many studies reported on contributory factors	Terminology used to describe contributory factors	Definition (could be about specific contributory factors e.g. organizational factors)	Methodology/theory specific to identify and classifying	Classification of the factors (e.g.,patient related)	Reported contributory factors

Medication errors				
Study ID	Terminology	Definition	Methodology for classifying medication errors	Classification of medication errors

Interventions to address contributory factors					
Study ID	Intervention recommended/applied	Characteristics	Delivery providers (e.g., nurse)	Theories/models/framework to develop the intervention	Outcomes of intervention

Appendix 4: PROSPERO registration protocol for phase two (systematic review)

Citation

Lina Naseralallah, Vibhu Paudyal, Derek Stewart, Malcom Price. Prevalence, nature and contributing factorsto medication errors in outpatient and ambulatory settings: a systematic review and meta-analysis.

PROSPERO 2021 CRD42021291006 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021291006

Review question

What is the prevalence of medication errors in hospital outpatient clinics and ambulatory care facilities?What is the nature (e.g. medication use process, incident type) of these errors?

What are the contributory factors leading to these errors?

Searches

Databases and search engines: MEDLINE, CINAHL, EMBASE, Google Scholar (20 pages)

Dates: from inception until Tuesday, November 2, 2021

Restrictions (as applicable to the database): English language, human data, full published articles

Types of study to be included

Any study design (e.g. observational studies, randomized controlled trials, qualitative studies) could beincluded on condition that the study reported one or more of the following:

1- Incidence or prevalence of medication errors in outpatient and ambulatory settings2- Nature or contributory factors for these medication errors

Condition or domain being studied

Medication errors in hospital outpatient clinics and ambulatory care facilities relevant to any clinical conditionor pharmacological class of drugs.

For the purpose of this study, we will adopt the National Coordinating Council for Medication Error Reportingand Prevention (NCCMERP) definition of medication errors “any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer”. We will also capture the definitions of medication errors used by individual studies.

Participants/population [1 change]

Patients (with no restriction on age, gender, or clinical specialty) who experienced medication errors inhospital outpatient clinics or ambulatory care facilities.

Intervention(s), exposure(s) [1 change]

We are not assessing a particular intervention and its impact on medication error; thus the presence of acertain intervention/exposure is not a requirement for studies to be included in this systematic review as would be the case in reviews of effectiveness or cost-effectiveness.

Where any intervention has been evaluated such as educational or technological, we will consider outcomesdata on medication errors before and after the interventions in both intervention and comparator groups. No restriction on the type of intervention will be applied as long as they reported medication errors rates, types, or contributing factors. Examples could be pharmacist-led intervention, educational activities, or electronic rescribing.

Comparator(s)/control [1 change]

We are not assessing a particular intervention and comparing it to usual care or another comparator; thus the presence of a certain comparator is not a requirement for studies to be included in this systematic reviewas would be the case in reviews of effectiveness or cost-effectiveness.

Where any intervention has been evaluated such as educational or technological, we will consider outcomesdata on medication errors before and after the interventions in both intervention and comparator groups. No restriction on the type of comparator will be applied as long as they reported medication errors rates, types, or contributing factors. Examples could be usual care or different software for electronic prescribing.

Main outcome(s)

Quantitative or quantitative outcomes related to the following:

Incidence and/or prevalence of medication errors

Classification of medication errors according to the stage of medication use process: prescribing, transcribing, administration and dispensing

Classification of medication errors according to incident type: we will adopt the categorization from a previously published study (Haque et al., 2021): not indicated, allergic reaction, wrong labeling, wrong quantity, patient self-administered error, incorrect patient, duplicate therapy, contraindication, wrong/omittedverbal patient direction, wrong dose/strength, wrong drug, missed drug/omission. If needed, we will consideradding new categories in case of emerging reoccurring events.

Contributary factors contributing to medication error according to Reason’s accident causation model

Active failure: slips (attention), lapses (memory), fumbles (execution), mistakes (decision making), and procedural violations (intentional rule breaking)

Latent conditions: system failures attributed to top level management decisions

Additional outcome(s)

None

Data extraction (selection and coding)

Two authors will independently screen the titles, abstracts, and full texts for eligibility. Discrepancies will beresolved by discussion with other team members. A data extraction tool will be created to abstract: study authors and year, country, study design, settings, study population characteristics, incidence/prevalence ofmedication errors, classification of medication errors, nature of medication errors and contributing factors (based on Reason's accident causation model).

Risk of bias (quality) assessment

Two raters will independently conduct the risk of bias assessment utilizing the following:

1- Quality assessment checklist for prevalence studies (Hoy et al., 2012): for incidence/prevalence data2- The Critical Appraisal Skills Programme (CASP) tool: for the rest of study designs

Consensus will be sought through discussion with other team members.

Strategy for data synthesis

For classification of medication errors, nature of medication errors and contributing factors data, a narrativeapproach to data synthesis will be employed, which will also include study characteristics tables to summarize relevant data according to the data extraction tool.

Quantitative synthesis will be carried out if the included studies are sufficiently homogenous. Where suitable,a meta-analysis will be conducted using Cochrane Collaboration Review Manager (RevMan) version 5.3, and a random-effects model will be used as clinical heterogeneity is expected to present between studies.

Heterogeneity will be quantified using the I^2 statistic and by reporting predictive distributions. If sufficientstudies are available we will examine potential small study effects using funnel plots.

Analysis of subgroups or subsets

Type of medication error based on the errors occurring at a given stage of the medication use process.These will include prescribing, dispensing, administration errors.

Contact details for further information

Lina Naseralallah lxn107@student.bham.ac.uk

Organisational affiliation of the review

School of Pharmacy, College of Medical and Dental Sciences, University of Birmingham, Birmingham, UK

Review team members and their organisational affiliations [1 change]

Ms Lina Naseralallah. School of Pharmacy, College of Medical and Dental Sciences, University ofBirmingham, Birmingham, UK

Dr Vibhu Paudyal. School of Pharmacy, College of Medical and Dental Sciences, University of Birmingham,Birmingham, UK

Professor Derek Stewart. College of Pharmacy, Qatar University, Doha, Qatar

Dr Malcom Price. Applied Health Research, University of Birmingham, Birmingham, UK

Type and method of review

Meta-analysis, Systematic review

Anticipated or actual start date

20 October 2021

Anticipated completion date

20 February 2022

Funding sources/sponsors

None

Language

English

Country

England, Qatar

Stage of review

Review Ongoing

Subject index terms status

Subject indexing assigned by CRD

Subject index terms

Ambulatory Care Facilities; Humans; Medication Errors; Outpatients; Prevalence

Date of registration in PROSPERO

16 November 2021

Date of first submission

12 November 2021

Stage of review at time of this submission

Stage	Started	Completed

Preliminary searches	Yes	No
Piloting of the study selection process	Yes	No
Formal screening of search results against eligibility criteria	Yes	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

Appendix 5: Full search strategy for phase two (systematic review)

1- Databases:

- Medline
- CINAHL
- EMBASE

Other search engines:

- Google Scholar (20 pages) on January 22, 2022

2- Search terms:

Two fields (connected with AND):

Medication errors:

- medication error [MeSH] OR ((medication* OR transcrib* OR prescrib* OR dispens* OR administ*) adj3 (incident* OR mistake* OR error*))

Setting:

- outpatient clinics, hospital [MeSH] OR ambulatory care [MeSH] OR ambulatory care facilities [MeSH] OR outpatients [MeSH] OR ((ambulatory OR outpatient*) adj3 (care* OR healthcare* OR clinic* OR service* OR department* OR center* OR facilit*))

3- Search from Medline: Date: Tuesday, November 2, 2021

Filter: English, Human

# ▲	Searches	Results	Type
1	medication error.mp. or Medication Error*/	1513	Advanced
2	((medication* or transcrib* or prescrib* or dispens* or administ*) adj3 (incident* or mistake* or error*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	16569	Advanced
3	1 or 2	16569	Advanced
4	outpatient clinics, hospital.mp. or Outpatient Clinics, Hospital/	15812	Advanced
5	ambulatory care.mp. or Ambulatory Care/	70244	Advanced
6	ambulatory care facilities.mp. or Ambulatory Care Facilities/	20664	Advanced
7	outpatients.mp. or Outpatient*/	57202	Advanced
8	((ambulatory or outpatient*) adj3 (care* or healthcare* or clinic* or service* or department* or center* or facilit*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	138199	Advanced
9	4 or 5 or 6 or 7 or 8	179736	Advanced
10	3 and 9	649	Advanced
11	limit 10 to (english language and humans)	585	Advanced

4- Search from EMBASE: Date: Tuesday, November 2, 2021

Filter: English, Human

- All MeSH terms were similar to Medline

# ▲	Searches	Results
1	medication error.mp. or Medication Error/	19744
2	((medication* or transcrib* or prescrib* or dispens* or administ*) adj3 (incident* or mistake* or error*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]	25993
3	1 or 2	25993
4	outpatient clinics, hospital.mp. or Outpatient Clinics, Hospital/	63966
5	ambulatory care.mp. or Ambulatory Care/	43795
6	ambulatory care facilities.mp. or Ambulatory Care Facilities/	63883
7	outpatients.mp. or Outpatient/	177086
8	((ambulatory or outpatient*) adj3 (care* or healthcare* or clinic* or service* or department* or center* or facilit*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]	226805
9	4 or 5 or 6 or 7 or 8	360442
10	3 and 9	1482
11	limit 10 to (english language and humans)	1292

5- Search from CINAHL: Date: Tuesday, November 2, 2021

Filter: English, Human

- CINAHL does not use adj3, so I replaced it with AND
- If the MeSH term from Medline is not available, we used the closest available subject heading from CINHAL. If we couldn't find any close subject heading, we searched as a key word (e.g. outpatient clinics, hospital was replaced by outpatient services as it was under this subject heading).

Search ID#	Search Terms	Search Options	Actions
S10	S3 AND S9	**Limiters** - English Language; Human **Expanders** - Apply equivalent subjects **Search modes** - Boolean/Phrase	View Results (938)
S9	S4 OR S5 OR S6 OR S7 OR S8	**Expanders** - Apply equivalent subjects **Search modes** - Boolean/Phrase	View Results (132,191)
S8	((ambulatory OR outpatient*) AND (care* OR healthcare* OR clinic* OR service* OR department* OR center* OR facilit*))	**Expanders** - Apply equivalent subjects **Search modes** - Boolean/Phrase	View Results (122,013)
S7	(MH "Outpatients")	**Expanders** - Apply equivalent subjects **Search modes** - Boolean/Phrase	View Results (48,470)
S6	(MH "Ambulatory Care Facilities")	**Expanders** - Apply equivalent subjects **Search modes** - Boolean/Phrase	View Results (8,537)
S5	(MH "Ambulatory Care")	**Expanders** - Apply equivalent subjects **Search modes** - Boolean/Phrase	View Results (13,235)
S4	(MH "Outpatient Service")	**Expanders** - Apply equivalent subjects **Search modes** - Boolean/Phrase	View Results (10,043)
S3	S1 OR S2	**Expanders** - Apply equivalent subjects **Search modes** - Boolean/Phrase	View Results (36,062)
S2	((medication* OR transcrib* OR prescrib* OR dispens* OR administ*) AND (incident* OR mistake* OR error*))	**Expanders** - Apply equivalent subjects **Search modes** - Boolean/Phrase	View Results (36,062)
S1	(MH "Medication Errors")	**Expanders** - Apply equivalent subjects	View Results (14,420)

Appendix 6: Data extraction sheets for phase two (systematic review)

Characteristics of included studies										
Study ID	Author, year	Country	Setting	Aim	Duration (start and end date)	Study design	Participants sampling and recruitment	Total number of participants	Population/data characteristics	Intervention characteristics (if any)

Studies reporting overall medication errors					
Study ID	Methodology specific to prevalence data	Duration for which prevalence data were collected	Total number of observations (denominator) – report for all	Number (%) of overall medication errors	Limitations

Studies reporting medication errors according to the medication use process						
Study ID	Type of medication errors according to the medication use process (report for all)	Methodology specific to prevalence data	Duration for which prevalence data were collected	Total number of observations (denominator) – report for all	Number (%) of errors (report for all)	Limitations

Studies reporting according to the type of prescribing errors (incident type)						
Study ID	Type of prescribing error according to the incident type (report for all)	Methodology specific to prevalence data	Duration for which prevalence data were collected	Total number of observations (denominator) – report for all	Number (%) of errors (report for all)	Limitations

Studies reporting severity classifications of medication errors			
Study ID	Methodology specific to severity classification	Type of severity classes reported	Number (%) of errors (report for all)

Studies reporting on the outcomes of implemented interventions					
Study ID	Post-intervention number of errors (report for all)	Total number of interventions/preventable errors	Methodology for intervention subclassification (if any)	Intervention subclassification (if any)	Acceptance rate

Studies reporting on contributory factors				
Study ID	Active failure (yes/no)	Types of active failure	Latent conditions (yes/no)	Types of latent conditions

Appendix 7: Tables

Table 1. Articles excluded at the full text screening stage for phase one (umbrella review)		
Number	**Title of the excluded review**	**Reason for exclusion**
1	12 h shifts and rates of error among nurses: A systematic review	Not focused on medication errors
2	A literature review of the individual and systems factors that contribute to medication errors in nursing practice	Not a systematic review
3	A Study on the effect of lecture and multimedia software on drug calculation and prescription: A systematic review	No investigation of contributory factors
4	A systematic literature review on strategies to avoid look-alike errors of labels	No investigation of contributory factors
5	A systematic review of clinical pharmacist interventions in paediatric hospital patients	No investigation of contributory factors
6	A systematic review of qualitative research on the contributory factors leading to medicine-related problems from the perspectives of adult patients with cardiovascular diseases and diabetes mellitus	Not focused on medication errors
7	A systematic review of the effectiveness of interruptive medication prescribing alerts in hospital CPOE systems to change prescriber behavior and improve patient safety	No investigation of contributory factors
8	A systematic review of the extent, nature and likely causes of preventable adverse events arising from hospital care	Not focused on medication errors
9	A systematic review of the prevalence and risk factors for adverse drug reactions in the elderly in the acute care setting	Not focused on medication errors
10	A systematic review of the types and causes of prescribing errors generated from using computerized provider order entry systems in primary and secondary care	Not focused on medication errors
11	Alert Types and Frequencies During Bar Code–Assisted Medication Administration	Not focused on medication errors
12	An individual patient data meta-analysis on factors associated with adverse drug events in surgical and non-surgical inpatients	Not focused on medication errors
13	An integrative review of method types used in the study of medication error during anaesthesia: implications for estimating incidence	No investigation of contributory factors
14	Bar code technology and medication administration error	No investigation of contributory factors
15	Barriers to implementation of medication error continuous quality improvement programs in community pharmacies: A systematic literature review	Conference proceeding
16	Contributing factors that influence medication errors in the prehospital paramedic environment: a mixed-method systematic review protocol	Conference proceeding
17	Direct Observation of Medication Errors in Critical Care Setting: A Systematic Review	No investigation of contributory factors
18	Do calculation errors by nurses cause medication errors in clinical practice? A literature review	Not a systematic review

19	Drug Administration Errors in Hospital Inpatients: A Systematic Review	No investigation of contributory factors
20	Drug-related Problems in Home-dwelling Older Adults: A Systematic Review	Not focused on medication errors
21	Drug-Related Problems in Hospitalised Patients with Chronic Kidney Disease: A Systematic Review	Not focused on medication errors
22	Errors in antibiotic transitions between hospital and nursing home: How often do they occur?	Not a systematic review
23	Errors in preparation and medication management in nursing professionals	Not a systematic review
24	Factors associated with medication administration errors and why nurses fail to report them	Not a systematic review
25	Factors contributing to medication errors: a literature review	Not a systematic review
26	Factors contributing to registered nurse medication administration error: a narrative review	Not a systematic review
27	Identification of an updated set of prescribing--safety indicators for GPs	No investigation of contributory factors
28	Identifying opioid medication error types, incidence and patient impact in adult oncology and palliative care settings: A systematic review	Conference proceeding
29	Identifying Risk Areas of Medication Administration Process for Developing an Interactive Three-Dimensional Game Intervention	Not a systematic review
30	Impact of pharmacist interventions on medication errors in hospitalized pediatric patients: a systematic review and meta-analysis	No investigation of contributory factors
31	Incidence and prevalence of prescribing errors in Saudi Arabia: A systematic study	No investigation of contributory factors
32	Incidence, nature and causes of medication errors in hospitalised patients in Middle Eastern countries: A systematic review	Conference proceeding
33	Interventions to reduce medication errors in adult medical and surgical settings: a systematic review	No investigation of contributory factors
34	Interventions to reduce nurses' medication administration errors in inpatient settings: A systematic review and meta-analysis	No investigation of contributory factors
35	Medication errors in neonatal care: A systematic review of types of errors and effectiveness of preventive strategies	No investigation of contributory factors
36	Medication errors in paediatric care: a systematic review of epidemiology and an evaluation of evidence supporting reduction strategy recommendations	No investigation of contributory factors
37	Medication errors with oral chemotherapies: Highlights from cases reported in the French Pharmacovigilance Database	Not a systematic review
38	Medication safety in acute care in Australia: where are we now? Part 1: a review of the extent and causes of medication problems 2002–2008	Not a systematic review
39	Medication safety programs in primary care: a scoping review	No investigation of contributory factors

40	Medicine use and medicine-related problems in patients with liver cirrhosis: a systematic review of quantitative and qualitative studies	Not focused on medication errors
41	Nurses' perceptions of the causes of medication errors: an integrative literature review	Not a systematic review
42	Patient safety in inpatient mental health settings: a systematic review	Not focused on medication errors
43	Prevalence and Nature of Medication Errors and Medication-Related Harm Following Discharge from Hospital to Community Settings: A Systematic Review	No investigation of contributory factors
44	Prevalence and Nature of Medication Errors and Preventable Adverse Drug Events in Paediatric and Neonatal Intensive Care Settings: A Systematic Review	No investigation of contributory factors
45	Prevalence and Risk Factors for Drug-Related Problems in People With Dementia Living in the Community: A Systematic Review and Meta-Analysis	Not focused on medication errors
46	Prevalence of computerized physician order entry systems-related medication prescription errors: A systematic review	No investigation of contributory factors
47	Prevalence, characteristics and predicting risk factors of adverse drug reactions among hospitalized older adults: A systematic review and meta-analysis	Not focused on medication errors
48	Prevalence, incidence and nature of prescribing errors in hospital inpatients: A systematic review	No investigation of contributory factors
49	Quantifying the burden of opioid medication errors in adult oncology and palliative care settings: A systematic review	No investigation of contributory factors
50	Systematic review of the safety of medication use in inpatient, outpatient and primary care settings in the Gulf Cooperation Council countries	Not focused on medication errors
51	Systematic review: Epidemiology, nature and interventions of hospital medication administration errors in paediatrics	Conference proceeding
52	Systematic review: Nurses' safety attitudes and their impact on patient outcomes in acute-care hospitals	Not focused on medication errors
53	The burden of medication errors and preventable adverse drug events in critically ill children: A systematic review	Conference proceeding
54	The causes of and factors associated with medication administration errors: A systematic review of empirical evidence	Conference proceeding
55	The incidence and nature of in-hospital adverse events: a systematic review	No investigation of contributory factors
56	The types and causes of medication errors when using computerized provider order entry systems in pediatrics: A systematic review	Conference proceeding
57	What is the burden of medication errors and adverse drug events in mental health hospitals? A systematic review	Conference proceeding

Table 2. Articles excluded at the full text screening stage for phase two (systematic review)		
Number	**Title of the excluded review**	**Reason for exclusion**
1	A cross-sectional study on prescribing and dispensing errors at a corporate hospital in South India	No isolation of adult outcomes
2	A prospective observational study of medication errors in general medicine department in a tertiary care hospital	Not focused on outpatient and ambulatory settings
3	Adverse events in psychiatry: A national cohort study in Sweden with a unique psychiatric trigger tool	Not focused on outpatient and ambulatory settings
4	An Internal Quality Improvement Collaborative Significantly Reduces Hospital-Wide Medication Error Related Adverse Drug Events	Not focused on outpatient and ambulatory settings
5	An observational study to evaluate the factors which influence the dispensing errors in the hospital pharmacy of a tertiary care hospital	Not focused on outpatient and ambulatory settings
6	Appropriateness of prescribing in selected healthcare facilities in Papua New Guinea	Not focused on medication errors
7	Clinical evaluation of pharmacists' interventions on multidisciplinary lung transplant outpatients' management: results of a 7-year observational study	No isolation of adult outcomes
8	Description of the role of pharmacist independent double checks during cognitive order verification of outpatient parenteral anti-cancer therapy	Not focused on medication errors
9	Descriptive analysis of medication errors reported to the Egyptian national online reporting system during six months	No isolation of adult outcomes
10	Drug errors and related interventions reported by united states clinical pharmacists: The american college of clinical pharmacy practice-based research network medication error detection, amelioration and prevention study	Not focused on outpatient and ambulatory settings
11	Epidemiology of adverse events and medical errors in the care of cardiology patients	Not focused on medication errors
12	Errors associated with outpatient computerized prescribing systems	Not focused on outpatient and ambulatory settings
13	Evaluation of faculty and non-faculty physicians' medication errors in outpatients' prescriptions in Shiraz, Iran	No isolation of adult outcomes
14	Frequency of ambulatory care adverse events in Latin American countries: the AMBEAS/PAHO cohort study	Not focused on medication errors
15	Frequency of and risk factors for medication errors by pharmacists during order verification in a tertiary care medical center	Not focused on outpatient and ambulatory settings
16	Frequency of medication errors in primary care patients with polypharmacy	Not focused on medication errors

17	Identification of medication errors through a monitoring and minimization program in outpatients in Colombia, 2018-2019	Not English
18	Impact of clinical pharmacy services on medication errors in a multispecialty hospital	Not focused on outpatient and ambulatory settings
19	Impacts of Pharmacists-Managed Oncology Outpatient Clinic on Resolving Drug-Related Problems in Ambulatory Neoplasm Patients: A Prospective Study in China	Not focused on medication errors
20	Medication errors and adverse drug reactions in psychiatry department: A prospective observational study	No full text
21	Medication errors in a health care facility in southern Saudi Arabia	Not focused on outpatient and ambulatory settings
22	Medication errors in Auvergne-Rhone-Alpes: A prospective pilot study led in collaboration by regional vigilance and support structures	Not English
23	Medication errors in outpatient care in Colombia, 2005-2013	Not focused on outpatient and ambulatory settings
24	Medication errors reported to the National Medication Error Reporting System in Malaysia: a 4-year retrospective review (2009 to 2012)	Not focused on outpatient and ambulatory settings
25	Medication incidents associated with outpatient computerized prescribing systems	No isolation of adult outcomes
26	Minimising prescription errors-a quality improvement project in the ophthalmology department in a tertiary referral hospital	Not focused on outpatient and ambulatory settings
27	Pharmacist's role in improving medication safety for patients in an allogeneic hematopoietic cell transplant ambulatory clinic	Not focused on outpatient and ambulatory settings
28	Potential risks in drug prescriptions to elderly: A cross-sectional study in the public primary health care system of Ourinhos micro-region, Brazil.	No full text
29	Prescription, Transcription and Administration Errors in Out- Patient Day Care Unit of a Regional Cancer Centre in South India	Not focused on outpatient and ambulatory settings
30	Prevalence of medication-related problems among patients with renal compromise in an Indian hospital	Not focused on outpatient and ambulatory settings
31	Prevalence, nature and potential preventability of adverse drug events - A population-based medical record study of 4970 adults	Not focused on outpatient and ambulatory settings
32	Prevention of medication errors in drug dispensation to outpatients, Colombia june 2014 to june 2015	Not English
33	Reducing Medical Errors in Primary Care Using a Pragmatic Complex Intervention	Not focused on medication errors

34	Strategies to Reduce Medication Errors in Ambulatory Practice	Not focused on medication errors
35	The impact of electronic prescription on reducing medication errors in an Egyptian outpatient clinic	No isolation of adult outcomes
36	Update on Drug-Related Problems in the Elderly	Not focused on medication errors
37	What Safety Events Are Reported For Ambulatory Care? Analysis of Incident Reports from a Patient Safety Organization	Not focused on medication errors

Appendix 8: Statistical analyses figures

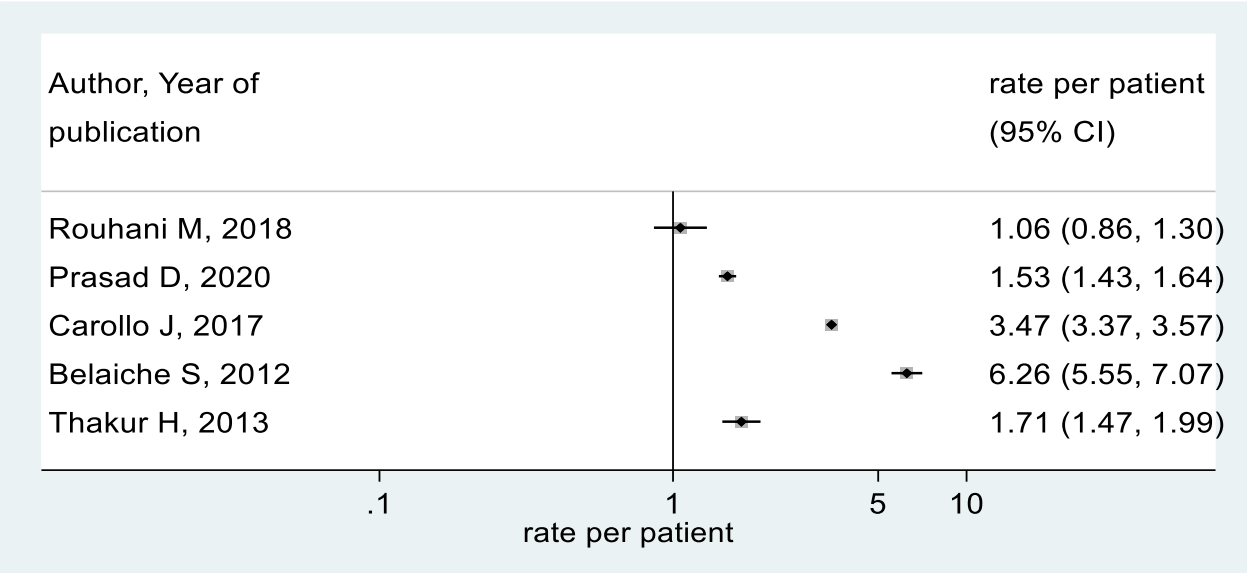

Figure 1. Forest plot of the rate of overall medication errors per patient

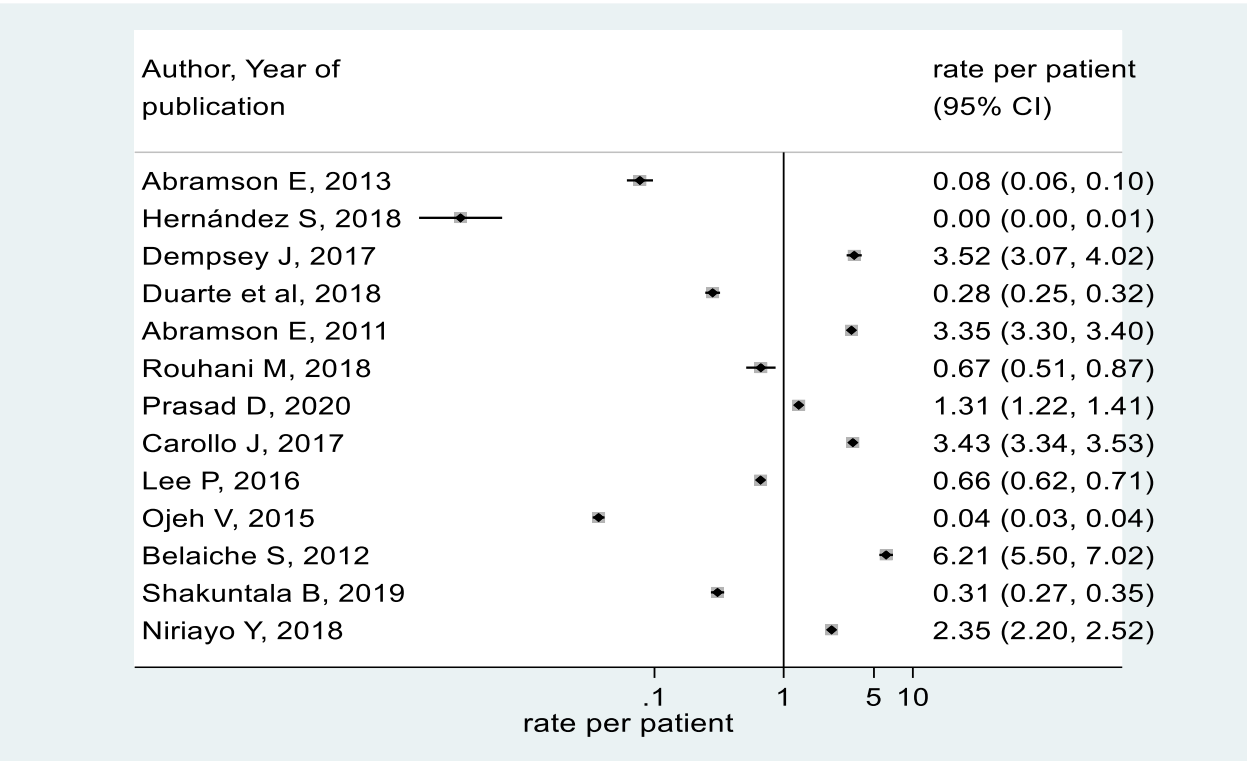

Figure 2. Forest plot of the rate of prescribing errors per patient

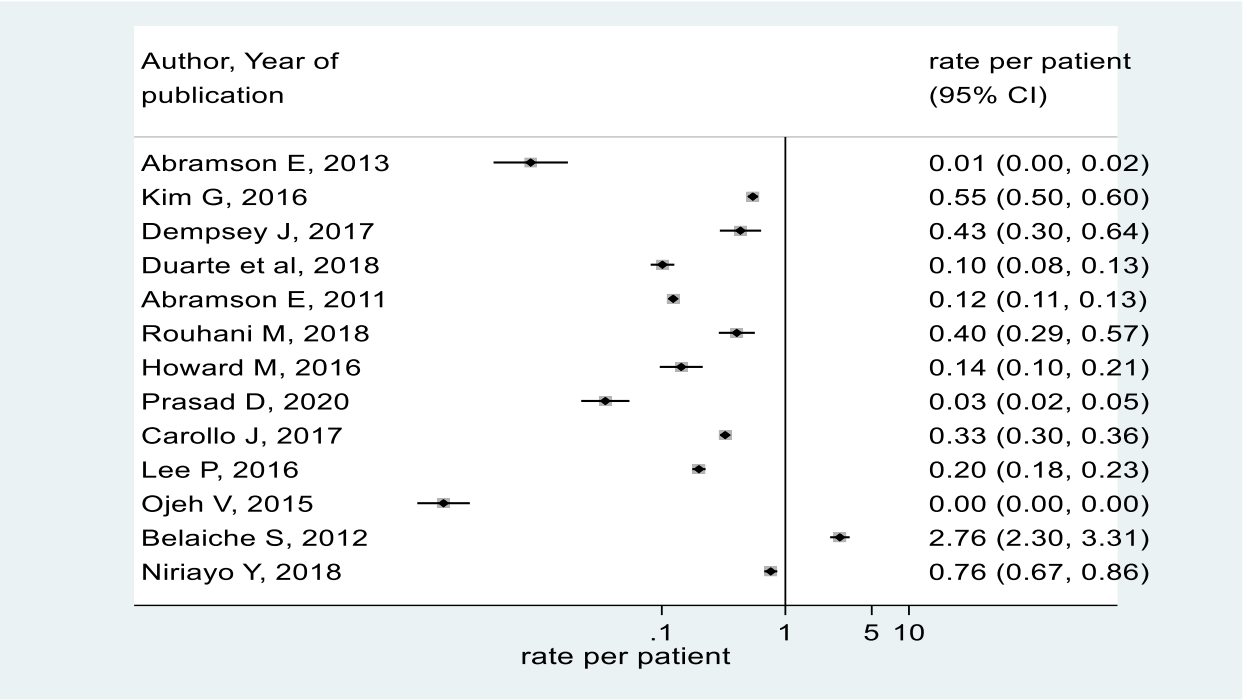

Figure 3. Forest plot of the rate of dosing errors per patient

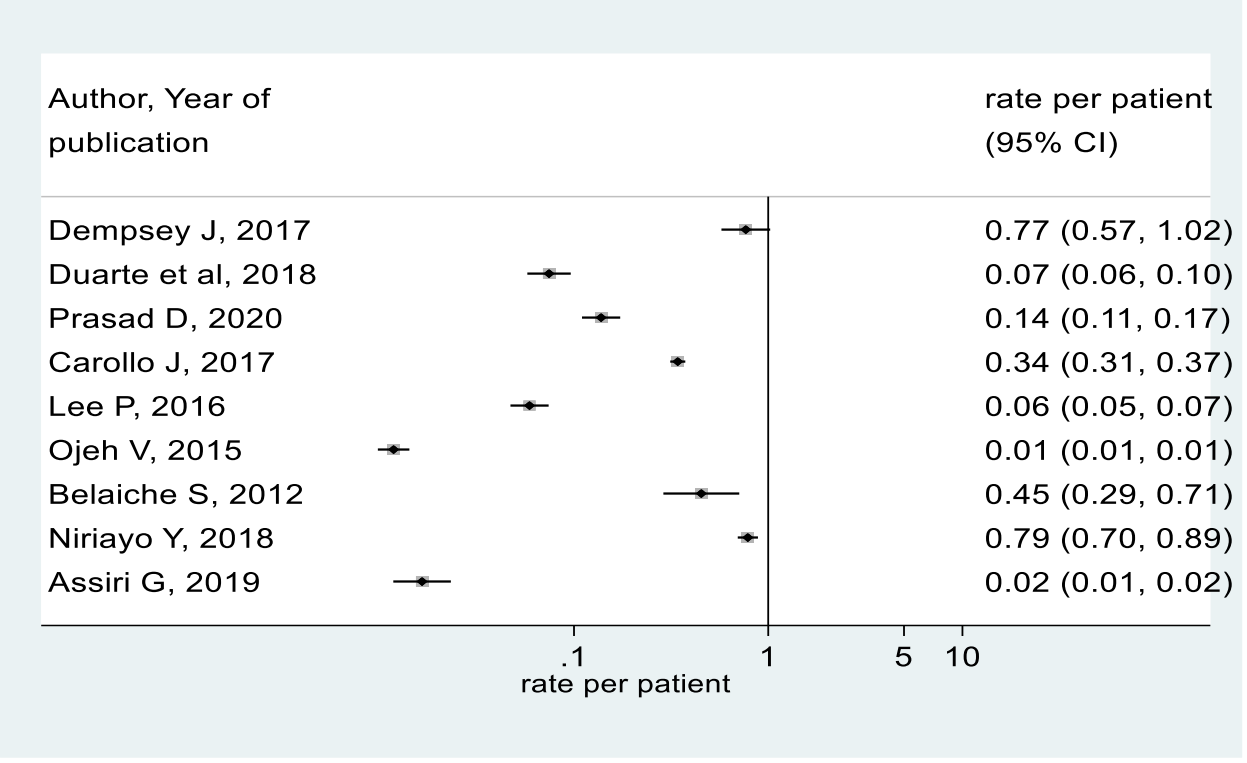

Figure 4. Forest plot of the rate of wrong/suboptimal errors per patient

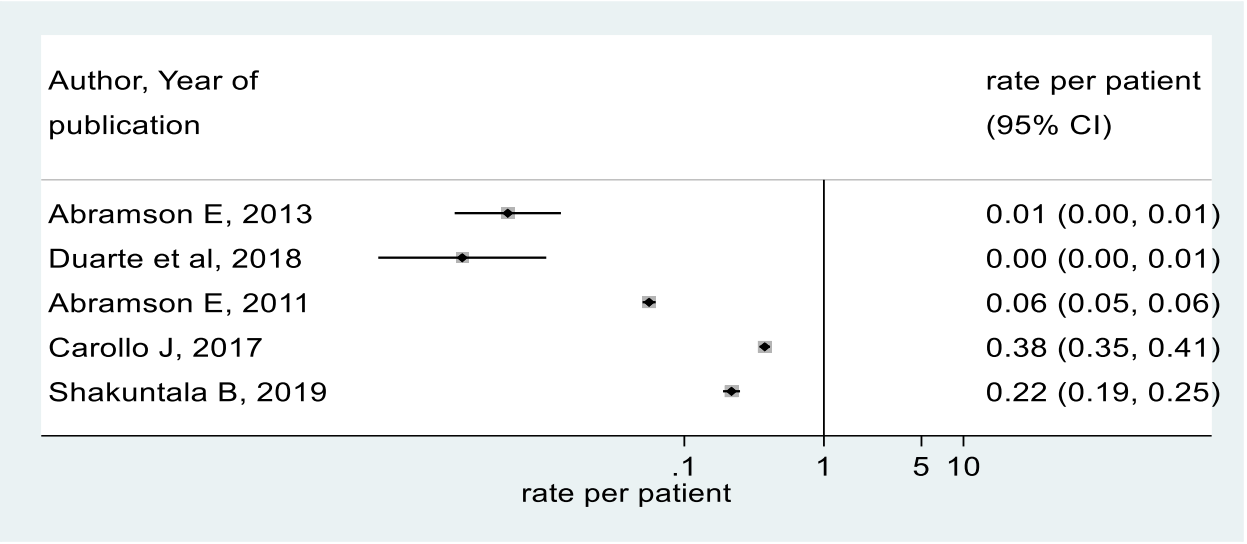

Figure 5. Forest plot of the rate of duration errors per patient

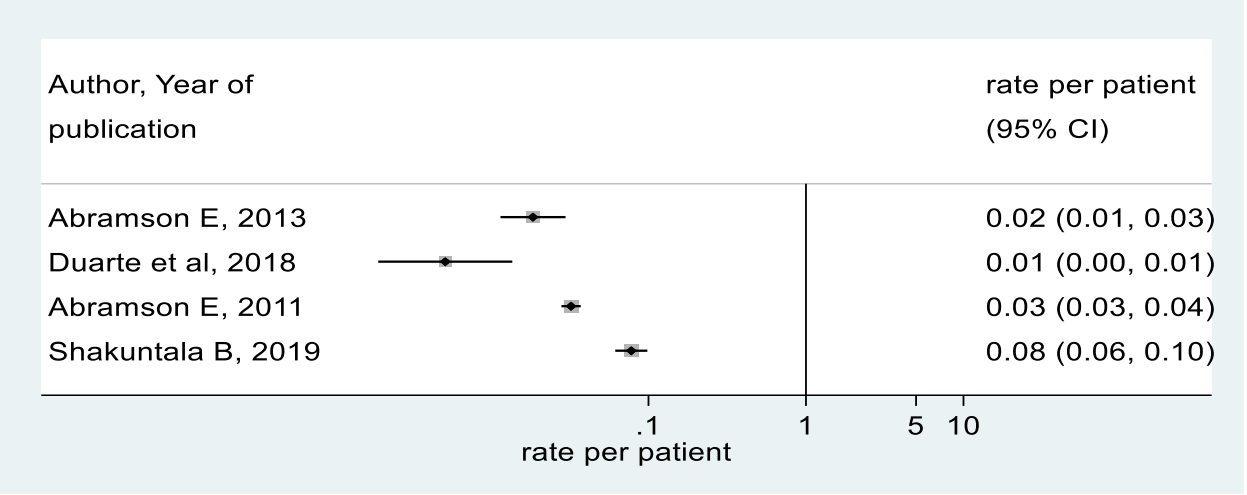

Figure 6. Forest plot of the rate of frequency errors per patient

Appendix 9: Assessment of the current reviews according to the AMSTAR2 tool

Table 1. Assessment of the umbrella review according to the AMSTAR 2 tool

1. Did the research questions and inclusion criteria for the review include the components of PICO?

For Yes:

✓ Population
✓ Intervention
✓ Comparator group
✓ Outcome

Optional (recommended)

 Timeframe for follow-up

✓ Yes
 No

2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?

For Partial Yes:
The authors state that they had a written protocol or guide that included ALL the following:

✓ review question(s)
✓ a search strategy
✓ inclusion/exclusion criteria
✓ a risk of bias assessment

For Yes:
As for partial yes, plus the protocol should be registered and should also have specified:

N/A a meta-analysis/synthesis plan, if appropriate, *and*
N/A a plan for investigating causes of heterogeneity
N/A justification for any deviation from the protocol

✓ Yes
 Partial Yes
 No

3. Did the review authors explain their selection of the study designs for inclusion in the review?

For Yes, the review should satisfy ONE of the following:

 Explanation for including only RCTs
 OR *Explanation for* including only NRSI
✓ OR *Explanation for* including both RCTs and NRSI

✓ Yes
 No

4. Did the review authors use a comprehensive literature search strategy?

For Partial Yes (all the following):

✓ searched at least 2 databases (relevant to research question)
✓ provided key word and/or search strategy
✓ justified publication restrictions (e.g. language)

For Yes, should also have (all the following):

✓ searched the reference lists / bibliographies of included studies
✗ searched trial/study registries
✓ included/consulted content experts in the field
✓ where relevant, searched

✓ Yes
 Partial Yes
 No

	for grey literature ✓ conducted search within 24 months of completion of the review	

5. Did the review authors perform study selection in duplicate?

For Yes, either ONE of the following: ✓ at least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include OR two reviewers selected a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder selected by one reviewer.	✓ Yes No

6. Did the review authors perform data extraction in duplicate?

For Yes, either ONE of the following: at least two reviewers achieved consensus on which data to extract from included studies ✓ OR two reviewers extracted data from a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder extracted by one reviewer.	✓ Yes No

7. Did the review authors provide a list of excluded studies and justify the exclusions?

For Partial Yes: ✓ provided a list of all potentially relevant studies that were read in full-text form but excluded from the review	For Yes, must also have: ✓ Justified the exclusion from the review of each potentially relevant study	✓ Yes Partial Yes No

8. Did the review authors describe the included studies in adequate detail?

For Partial Yes (ALL the following): ✓ described populations ✓ described interventions N/A described comparators ✓ described outcomes ✓ described research designs	For Yes, should also have ALL the following: ✓ described population in detail ✓ described intervention in detail (including doses where relevant) N/A described comparator in detail (including doses where relevant) ✓ described study's setting N/A timeframe for follow-up	✓ Yes Partial Yes No

9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?

RCTs

For Partial Yes, must have assessed RoB from	For Yes, must also have assessed RoB from:	*None of the identified studies were RCTs; hence not applicable*
□ unconcealed allocation, *and* □ lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective outcomes such as all-cause mortality)	□ allocation sequence that was not truly random, *and* □ selection of the reported result from among multiple measurements or analyses of a specified outcome	□ Yes □ Partial Yes □ No □ Includes only NRSI

NRSI

For Partial Yes, must have assessed RoB:	For Yes, must also have assessed RoB:	
✓□ from confounding, *and* ✓□ from selection bias	✓□ methods used to ascertain exposures and outcomes, *and* ✓□ selection of the reported result from among multiple measurements or analyses of a specified outcome	✓ Yes □ Partial Yes □ No □ Includes only RCTs

10. Did the review authors report o n the sources of funding for the studies included in the review?

For Yes

✓□ Must have reported on the sources of funding for individual studies included in the review. Note: Reporting that the reviewers looked for this information was not reported by study authors also qualifies

✓ Yes
□ No but it

11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?

RCTs

For Yes:

□ The authors justified combining the data in a meta-analysis
□ AND they used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present.
□ AND investigated the causes of any heterogeneity

□ Yes
□ No
✓ No meta-analysis conducted

For NRSI

For Yes:

- □ The authors justified combining the data in a meta-analysis
  - □ AND they used an appropriate weighted technique to combine study results, adjusting for heterogeneity if present
  - □ AND they statistically combined effect estimates from NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adjusted effect estimates were not available
  - □ AND they reported separate summary estimates for RCTs and NRSI separately when both were included in the review

□ Yes
□ No
✓ No meta-analysis conducted

12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?

For Yes:

- □ included only low risk of bias RCTs
- □ OR, if the pooled estimate was based on RCTs and/or NRSI at variable RoB, the authors performed analyses to investigate possible impact of RoB on summary estimates of effect.

□ Yes
□ No
✓ No meta-analysis conducted

13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?

For Yes:

- □ included only low risk of bias RCTs
- ✓ OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results

✓ Yes
□ No

14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?

For Yes:

- □ There was no significant heterogeneity in the results
- ✓ OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review

✓ Yes
□ No

15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?

For Yes:

- □ performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias

□ Yes
□ No
✓ No meta-analysis conducted

16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?

For Yes:

✓ The authors reported no competing interests OR

☐ The authors described their funding sources and how they managed potential conflicts of interest

✓ Yes

☐ No

N/A: not applicable

Table 2. Assessment of the systematic review according to the AMSTAR 2 tool

1. Did the research questions and inclusion criteria for the review include the components of PICO?

For Yes:

✓ Population
✓ Intervention
✓ Comparator group
✓ Outcome

Optional (recommended)

☐ Timeframe for follow-up

✓ Yes
☐ No

2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?

For Partial Yes:
The authors state that they had a written protocol or guide that included ALL the following:

✓ review question(s)
✓ a search strategy
✓ inclusion/exclusion criteria
✓ a risk of bias assessment

For Yes:
As for partial yes, plus the protocol should also have specified:

✓ a meta-analysis/synthesis plan, if appropriate, *and*
✓ a plan for investigating causes of heterogeneity
N/A justification for any deviation from the protocol

☐
☐

✓Yes
Partial Yes
No

3. Did the review authors explain their selection of the study designs for inclusion in the review?

For Yes, the review should satisfy ONE of the following:

☐ *Explanation for* including only RCTs
☐ OR *Explanation for* including only NRSI
✓ OR *Explanation for* including both RCTs and NRSI

✓ Yes
☐ No

4. Did the review authors use a comprehensive literature search strategy?

For Partial Yes (all the following):

✓ searched at least 2 databases (relevant to research question)
✓ provided key word and/or search strategy
✓ justified publication restrictions (e.g. language)

For Yes, should also have (all the following):

✓ searched the reference lists / bibliographies of included studies
✗ searched trial/study registries
✓ included/consulted content experts in the field
✓ where relevant, searched for grey literature
✓ conducted search

☐ Yes
✓ Partial Yes
☐ No

within 24 months of completion of the review	

5. Did the review authors perform study selection in duplicate?

For Yes, either ONE of the following: ✓ at least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include OR two reviewers selected a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder selected by one reviewer.	✓ Yes No

6. Did the review authors perform data extraction in duplicate?

For Yes, either ONE of the following: at least two reviewers achieved consensus on which data to extract from included studies ✓ OR two reviewers extracted data from a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder extracted by one reviewer.	✓ Yes No

7. Did the review authors provide a list of excluded studies and justify the exclusions?

For Partial Yes: ✓ provided a list of all potentially relevant studies that were read in full-text form but excluded from the review	For Yes, must also have: ✓ Justified the exclusion from the review of each potentially relevant study	✓ Yes Partial Yes No

8. Did the review authors describe the included studies in adequate detail?

For Partial Yes (ALL the following): ✓ described populations ✓ described interventions ✓ described comparators ✓ described outcomes ✓ described research designs	For Yes, should also have ALL the following: ✓ described population in detail ✓ described intervention in detail (including doses where relevant) ✓ described comparator in detail (including doses where relevant) ✓ described study's setting N/A timeframe for follow-up	✓ Yes Partial Yes No

9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?

RCTs For Partial Yes, must have assessed RoB from □ unconcealed allocation, *and* □ lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective outcomes such as all-cause mortality)	For Yes, must also have assessed RoB from: □ allocation sequence that was not truly random, *and* □ selection of the reported result from among multiple measurements or analyses of a specified outcome	*None of the identified studies were RCTs; hence not applicable* □ Yes □ Partial Yes □ No □ Includes only NRSI
NRSI For Partial Yes, must have assessed RoB: ✓□ from confounding, *and* ✓□ from selection bias	For Yes, must also have assessed RoB: ✓□ methods used to ascertain exposures and outcomes, *and* ✓□ selection of the reported result from among multiple measurements or analyses of a specified outcome	✓ Yes □ Partial Yes □ No □ Includes only RCTs

10. Did the review authors report on the sources of funding for the studies included in the review?

For Yes ✓ Must have reported on the sources of funding for individual studies included review. Note: Reporting that the reviewers looked for this information was not reported by study authors also qualifies	✓ Yes in the □ No but it

11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?

RCTs For Yes: □ The authors justified combining the data in a meta-analysis □ AND they used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present. □ AND investigated the causes of any heterogeneity	□ Yes □ No ✓ No meta-analysis conducted

For NRSI

For Yes:

- □ The authors justified combining the data in a meta-analysis
  - □ AND they used an appropriate weighted technique to combine study results, adjusting for heterogeneity if present
    - □ AND they statistically combined effect estimates from NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adjusted effect estimates were not available

N/A □ AND they reported separate summary estimates for RCTs and NRSI separately when both were included in the review

□ Yes
□ No
✓ No meta-analysis conducted

12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?

For Yes:

- □ included only low risk of bias RCTs
  - □ OR, if the pooled estimate was based on RCTs and/or NRSI at variable RoB, the authors performed analyses to investigate possible impact of RoB on summary estimates of effect.

□ Yes
□ No
✓No meta-analysis conducted

13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?

For Yes:

- □ included only low risk of bias RCTs
- ✓ OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results

✓ Yes
□ No

14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?

For Yes:

- □ There was no significant heterogeneity in the results
- ✓□ OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review

✓ Yes
□ No

15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?

For Yes:

- □ performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias

□ Yes
□ No
✓ No meta-analysis conducted

16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?

For Yes:

✓ The authors reported no competing interests OR

☐ The authors described their funding sources and how they managed potential conflicts of interest

✓ Yes

☐ No

N/A: not applicable